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Ambient Water Quality Criteria: Arsenic

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Section 304(a) of the Clean Water Act (33 U.S.C. 1314(a)), requires EPA to publish and periodically update water quality criteria. These criteria are to reflect the latest scientific knowledge on the identifiable effects of pollutants on public health and welfare, aquatic life, and recreation. This report presents water quality criteria for arsenic. It presents concentration criteria for the protection of fresh water and saltwater aquatic life. It presents 'safe' concentrations for humans, and in the case of suspect or proven carcinogens, gives various levels of incremental cancer risk. A section 304(a) water quality criterion is a qualitative or quantitative estimate of the concentration of a water constituent or pollutant in ambient waters which, when not exceeded, will ensure a water quality sufficient to protect a specified water use. Under the Act a criterion is a scientific entity, based solely on data and scientific judgment. It does not reflect considerations of economic or technological feasibility nor is it a water quality standard and in itself has no , ...

KEYWORDS: *Water quality, *Toxicology, *Arsenic, *Water pollution effects(Humans), *Water pollution effects(Animals), *Toxic substances.

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PB 292420

ARSENIC

Ambient Water Quality Criteria

Criteria and Standards Division
Office of Water Planning and Standards
U.S. Environmental Protection Agency
Washington, D.C.

CRITERION DOCUMENT

ARSENIC AND COMPOUNDS

Criteria

Aquatic Life

For arsenic, the criterion to protect freshwater aquatic life, as derived using the Guidelines, is 57 µg/l as a 24 hour average and the concentration should never exceed 130 µg/l at any time.

For arsenic, the criterion to protect saltwater aquatic life, as derived using procedures other than the Guidelines, is 29 µg/l as a 24 hour average and the concentration should never exceed 67 µg/l at any time.

Human Health

For the maximum protection of human health from the potential carcinogenic effects of exposure to arsenic through ingestion of water and contaminated aquatic organisms, the ambient water concentration is zero. Concentrations of arsenic estimated to result in additional lifetime cancer risks ranging from no additional risk to an additional risk of 1 in 100,000 are presented in the Criterion Formulation section of this document. The Agency is considering setting criteria at an interim target risk level in the range of 10^{-5}, 10^{-6}, or 10^{-7} with corresponding criteria of .02 µg/l, .002 µg/l, and .0002 µg/l, respectively.

Introduction

Arsenic is a naturally occurring element often referred to as a metal, although chemically classified as a metalloid. Arsenic and its compounds are used in the manufacturing of glass, cloth, and electrical semiconductors, as fungicides and wood preservatives, as growth stimulants for plants and animals, as well as in veterinary applications (U.S. EPA, 1976b). The United States consumes half of the world production of arsenic, or about 37,500 tons per year, and produces about 18,000 tons per year itself. The principal emission source for arsenic in the United States is thought to be coal-fuel power plants, which emit approximately 3,000 tons of arsenic per year (Nelson, 1977).

Environmental concentrations of arsenic have been reported at 5 mg per kg in the earth's crust (U.S. EPA, 1976a). Arsenic is found also in air and in all living organisms. Analysis of 1,577 U.S. surface waters showed arsenic to be present in 87 samples, with concentrations ranging from 5 to 336 µg As/l and a mean level of 64 ug As/l (Kopp, 1969). Bowen (1966) reported 3.0 µg/l in sea water.

A member of Group VB of the periodic table, arsenic has five electrons in its outer shell, giving rise to the oxidation states of +5, +3, 0, and -3. Arsenic as a free element (0) is rarely encountered in natural waters. Soluble inorganic arsenate (+5) predominates under normal conditions since it is thermodynamically more stable in water than arsenite (+3) (Ferguson and Gavis, 1972). Elemental arsenic is a gray, crystalline material with a molecular weight of 74.92, a density of 5.727, a melting point (at 28 atmospheres) of 817 degrees C, and a boiling point (sublime) of 613 degrees C (Weast, 1975). The low toxicity of elemental arsenic is attributed to its virtual insolubility in water or in the body fluids (U.S. EPA, 1976b).

The largest class of arsenic compounds are the organics, which are not naturally occurring. The two most common organic arsenic compounds are the arsonic acids, $R - \overset{\overset{O}{\|}}{\underset{\underset{OH}{|}}{As}} - OH$, and the arsinic acids, $R - \overset{\overset{O}{\|}}{\underset{\underset{R'}{|}}{As}} - OH$, where R and R' refer to a variety of organic (alkyl) groups (U.S. EPA, 1976b). The organic arsenic compounds considered to be of environmental importance are those containing methyl groups, the aromatic arsenic derivatives employed as feed additives and in veterinary medicine, and others which may have importance in biological systems (U.S. EPA, 1976a).

Arsenic forms a complete series of trihalides, while arsenic(V) fluoride is the only simple pentahalide known. All of the arsenic halides are covalent compounds that hydrolyze in the presence of water (Standen, 1967). Additional information on inorganic arsenic compounds is given in Table 1.

TABLE 1

Properties of some inorganic arsenic compounds (Standen, 1967; U.S. EPA, 1976a,b)

Compound	Formula	Water Solubility	Specific Properties
Arsenic trioxide	As_2O_3	12×10^6 µg/l @ 0 deg.C 21×10^6 µg/l @ 25 deg.C	Dissolves in water to form arsenious acid (H_3AsO_3: $K = 8\times10^{-10}$ @ 25 deg.C)
Arsenic pentoxide	As_2O_5	2300×10^6 µg/l @ 20 deg. C	Dissolves in water to form arsenic acid (H_3AsO_4: $K_1 = 2.5\times10^{-4}$ $K_2 = 5.6\times10^{-8}$; $K_3 = 3\times10^{-13}$)
Arsenic hydride	AsH_3	20 ml/100 g cold water	This compound and its methyl derivatives are considered to be the most toxic.
Arsenic(III) sulfide	As_4S_6	520 µg/l @ 18 deg. C	Burns in air forming arsenic trioxide and sulfur dioxide; occurs naturally as orpiment.
Arsenic sulfide	As_4S_4		Occurs naturally realgar.
Arsenic(V) sulfide	As_4S_{10}	1400 µg/l @ 0 deg.C	

Conditions of low pH, low Eh (standard oxidation-reduction potential) and low dissolved oxygen in water favor the formation of lower oxidation state arsenicals such as arsenite (+3) and arsine (-3) whereas more basic, oxygenated waters result in an increase in the percentage of arsenic present in the pentavalent state. The reducing action of certain organisms may also cause arsenite to be the predominate form. In waters of high organic content, a considerable amount of arsenic may be bound to colloidal humic matter (Ferguson and Gavis, 1972).

Both arsenate and arsenite can be removed from the water column by coprecipitation or adsorption onto iron oxides (LaPeintre, 1954; Gupta and Ghosh, 1953). Arsenate species can also be removed by adsorption onto aluminum hydroxide and clays, while arsenite is readily adsorbed onto metal sulfides (Ferguson and Gavis, 1972).

Oxidation of arsenite to arsenate occurs slowly at neutral pH's (faster in strongly acid or alkaline solutions), while methylation of arsenic to methyl and dimethylarsine by methanogenic bacteria is know to occur (McBride and Wolfe, 1971).

Arsenic has been shown to be toxic to both vertebrate and invertebrate freshwater aquatic organisms. Cladocerans have been reported to be more sensitive than fish to arsenic. However, certain invertebrates such as stoneflies appear to be more tolerant of arsenic than are fish.

There is a paucity of arsenic toxicity data for saltwater organisms. However, several marine studies reported LC50 values generally lower than those reported for comparable freshwater studies.

Arsenic has been shown to bioconcentrate in both fresh and saltwater organisms.

Although no animal experiments have demonstrated carcinogenicity of arsenic, several have shown that sodium arsenate induces developmental malformations in a variety of test animals including chick embryos, hamsters, rats and mice (Ancel, 1946; Ridgeway and Karnovsky, 1952; Ferm and Carpenter, 1968; Hood and Bishop, 1972; Beaudoin, 1974).

Data on exposure of humans points to a causal relationship between skin cancer and high level exposures to inorganic arsenic compounds (Tseng, et al. 1968). In addition, Browning (1961) reported the symptoms of acute arsenic poisoning by ingestion to be abdominal pain and vomiting, while acute poisoning by inhalation produces giddiness, headache, extreme general weakness and, later, nausea, vomiting, colic, diarrhea, and pains in the limbs.

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AQUATIC LIFE TOXICOLOGY*

FRESHWATER ORGANISMS

Introduction

Arsenical compounds are found in all living organisms including those in aquatic systems. Although major sources of arsenic in the environment are industrial, such as the smelting of non-ferrous ores and coal-fired power plants using arsenic-rich coal, substantial arsenic contamination of water can occur from the improper use of arsenical pesticides.

Arsenic in water is stable in four oxidation states (+5, +3, 0, and -3) depending upon chemical conditions. Arsenic as the free element (0) is rarely encountered in natural waters. Soluble inorganic arsenate (+5) predominates under normal conditions since it is thermodynamically more stable in water than arsenite (+3). Conditions of low pH, low Eh (standard oxidation-reduction potential) and low dissolved oxygen in water favor the formation of lower oxidation state arsenicals such as arsenite and arsine

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life [43 FR 21506 (May 18, 1978) and 43 FR 29028 (July 5, 1978)] and the Methodology Document in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are the calculations for deriving various measures of toxicity as described in the Guidelines.

(-3) whereas more basic, oxygenated waters result in an increase in the percentage of arsenic present in the pentavalent state. The reducing action of certain organisms may also cause arsenite to be the predominant form. In waters of high organic content, a considerable amount of arsenic may be bound to colloidal humic matter.

Inorganic arsenic can be converted to organic alkyl-arsenic acids (+3 and +5) and to the methylated arsines (-3) under anaerobic conditions, although biomethylation may occur under aerobic conditions as well. Methylated arsines appear to be volatile and sparingly soluble.

Arsenic forms kinetically stable bonds to sulfur and carbon in organic compounds. Like mercury, arsenic (+3) reacts with sulfhydryl groups of proteins and enzyme inactivation by this mechanism appears to be the primary mode of arsenic toxicity. Arsenate does not react with sulfhydryl groups.

Although considerable information has been published on arsenic and freshwater aquatic organisms, knowledge of its toxicity is less than complete since much of the work has been devoted to monitoring or field assessment studies. Many studies involving arsenic did not provide data that were useful for deriving a water quality criterion. Virtually no studies of chronic effects of arsenic to fish exist and only two references dealing with arsenic bioconcentration accurately reported exposure concentrations so bioconcentration factors could be calculated.

The present data base is somewhat limited and does not allow for discussion of the effects of water quality characteristics on toxicity or relative toxicity of the various chemical forms of arsenic. The majority of the toxicity tests have been conducted with arsenite (+3) and few data are available on arsenate (+5) or organic arsenicals. Some arsenite was probably converted to arsenate during the toxicity tests. All results are expressed as arsenic.

Acute Toxicity

The LC50 values for nine species of fish are shown in Table 1. From the 14 tests, seven static and seven flow-through values were obtained. Adjustments for test duration were needed in three instances.

Arsenic toxicity varied greatly with different species and within the same species of fish (Table 1). The lowest adjusted LC50 value (Hughes and Davis, 1967) was approximately 500 times lower than the highest value (Sorensen, 1976a). The LC50 values for bluegills (Cardwell, et al. 1976 and Hughes and Davis, 1967) alone were about 300 times different from each other. These large differences were due mainly to the low acute value given for bluegills (Hughes and Davis, 1967, Table 1) in which a specialized granular formulation of sodium arsenite was used. This was found to be more toxic than other formulations previously tested. Comparisons of the highest and lowest adjusted acute values without this value showed differences of approximately 8 times between species and 5 times for tests with bluegills. There was no reason, however, to question the validity of this value so as to delete it from the data base. Although tests were conducted in both hard and soft water, hardness as indicated by Inglis and Davis (1972) did not appear to affect the toxicity of arsenic. No significant difference in toxicity was found by these authors for comparative tests with bluegills in water of hardness ranging from 53 to 368 mg/l as $CaCO_3$. Comparison of LC50 values for fingerling and juvenile channel catfish (Clemens and Sneed, 1959 and Cardwell et al., 1976) and for bluegills (Hughes and Davis, 1967 and Cardwell, et al. 1976) show that early life stages of fish may be more sensitive to arsenic than later stages. This is in agreement with work reported by Sorensen (1976a) for green sunfish and Gilderhus (1966) for bluegills studied in outdoor ponds.

Other comparisons of the adjusted data show that the seven static tests yielded a slightly lower mean LC50 value for fish than the seven flow-through tests but significant differences could not be determined due to the wide diversity of responses.

When the geometric mean of all the values in Table 1 is divided by the sensitivity factor of 3.9, the LC50 value calculated to be equal or less than the LC50 value for 95 percent of the species is higher (4,400 ug/l) than only one value out of the 14, suggesting a reasonable fit of the data to procedures in the Guidelines for species sensitivity. The Final Fish Acute Value is 4,400 ug/l.

Acute static toxicity tests have been conducted for four invertebrate species, three daphnid species and one aquatic insect (Table 2). From these data, Daphnia sp. are more than twice as sensitive to arsenic as stoneflies even after a shorter period of exposure. Values for Daphnia sp. are lower than those for all but one of the acute tests with fish, indicating that these species are more sensitive to arsenic than fish on an acute basis. The LC50 value reported for stoneflies was slightly higher than the geometric mean of the acute values for fish suggesting aquatic insects may be more tolerant of arsenic.

When the geometric mean of the data is divided by the sensitivity factor of 21, the LC50 value calculated is approximately one-fifth of the lowest LC50 value in Table 2. The Final Invertebrate Acute Value is 130 µg/l. The sensitivity factor seems reasonable considering the range in LC50 values and the fact that only 4 species have been tested.

Since the Final Invertebrate Acute Value of 130 µg/l is lower than the Final Fish Acute Value of 4,400 µg/l, the Final Acute Value for freshwater aquatic life is 130 µg/l.

Chronic Toxicity

Only one chronic test has been conducted with freshwater organisms and arsenic (Table 3). One life cycle chronic test with Daphnia magna (Biesinger and Christensen, 1972) resulted in a chronic value of 853 µg/l. A comparison of the adjusted LC50 value from the same test shows that the acute toxicity value is about seven times higher than the value for chronic toxicity. The chronic value divided by the sensitivity factor (5.1) from the Guidelines gives a 95 percent species protection concentration of 170 µg/l, the Final Invertebrate Chronic Value. This concentration is higher than the Final Invertebrate Acute Value. This unlikely relationship is due to two factors: the chronic test was conducted with Daphnia magna, which is one of the more resistant species (Table 2), and the species sensitivity factor used to divide the geometric mean values is larger (21) for the acute tests than that (5.1) used for the chronic tests.

Plant Effects

The effects of arsenic on five species of aquatic plants (Table 4) was obtained from two studies in outdoor farm ponds. Four species of algae and one species of submerged plants were used. The lowest plant value was 2,300 ug/l, the Final Plant Value.

Residues

Bioconcentration factors were calculated by Spehar, et al. (manuscript) for five invertebrate species and two species of fish (Table 5). A bioconcentration factor of less than 1 was obtained for amphipods since residues were less than the detection limit. In the same study a bioconcentration factor of zero was reported for rainbow trout because concentrations in the exposed fish were the same as in the controls after a 28-day exposure period. Daphnia magna, snails, and stoneflies had slightly higher residues than trout tested under the same conditions indicating that lower aquatic forms may accumulate some arsenic. A bioconcentration factor of four was obtained for bluegills in another study (U.S. EPA, 1978). The half-life of this element in bluegill tissues was one day. The low bioconcentration and short biological half-life of arsenic in fish tissue suggest no residue problem will occur at exposure concentrations that are not directly toxic.

No Residue Limited Toxicant Concentration (RLTC) could be determined since no maximum permissible tissue concentration for arsenic is available.

Of the four values, the Final Fish Chronic Value (no data), Final Invertebrate Chronic Value (170 µg/l), Final Plant Value (2,300 µg/l) and the RLTC (no data) the Final Invertebrate Chronic Value of 170 µg/l becomes the Final Chronic Value.

Miscellaneous

Data on other toxicological effects (Table 6) show that there is a wide range of sensitivity of invertebrate and fish species to arsenic. Comparison of these data for fish with the fish acute values indicate that in almost all cases arsenic toxicity is increased with increased length of exposure. This assumption could not be made with the invertebrate data due to the large variability in responses. Water temperature also appears to influence arsenic toxicity. Sorensen (1976c) found that higher water temperature decreased the median lethal time (LT50) of green sunfish (Table 6) after exposure to two concentrations of arsenic.

No data in the table indicate adverse effects lower than the Final Chronic Value of 170 µg/l.

CRITERION FORMULATION

Freshwater - Aquatic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures. All concentrations herein are expressed in terms of arsenic.

Final Fish Acute Value = 4,400 µg/l
Final Invertebrate Acute Value = 130 µg/l
Final Acute Value = 130 µg/l
Final Fish Chronic Value = not available
Final Invertebrate Chronic Value = 170 µg/l
Final Plant Value = 2,300 µg/l
Residue Limited Toxicant Concentration = not available
Final Chronic Value = 170 µg/l
0.44 x Final Acute Value = 57 µg/l

The maximum concentration of arsenic is the Final Acute Value of 130 ug/l which is based on the more acutely sensitive invertebrate organisms. Since 0.44 times the Final Acute Value is lower than the Final Chronic Value (170 µg/l), the former is the 24-hour average concentration.

CRITERION: For arsenic the criterion to protect freshwater aquatic life as derived using the Guidelines is 57 µg/l as a 24-hour average and the concentration should not exceed 130 µg/l at any time.

Table 1. Freshwater fish acute values for arsenic***

Organism	Bioassay Method*	Test Conc.**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (µg/l)	Adjusted LC50 (µg/l)	Reference
Rainbow trout (juvenile), Salmo gairdneri	FT	M	-	96	10,800	10,800	Hale, 1977
Brook trout (adult) Salvelinus fontinalis	FT	M	140-152	96	14,964	14,964	Cardwell, et al. 1976
Goldfish (juvenile), Carassius auratus	FT	M	140-152	96	26,042	26,042	Cardwell, et al. 1976
Spottail shiner, Notropis hudsonius	S	M	-	72	27,000	17,636	Boschetti & McLoughlin, 1957
Fathead minnow (juvenile), Pimephales promelas	FT	M	140-152	96	15,660	15,660	Cardwell, et al. 1976
Channel catfish (juvenile), Ictalurus punctatus	FT	M	140-152	96	18,096	18,096	Cardwell, et al. 1976
Channel catfish (fingerling), Ictalurus punctatus	S	U	-	96	15,022	8,213	Clemens & Sneed, 1959
Flagfish (fry), Jordanella floridae	FT	M	140-152	96	28,130	28,130	Cardwell, et al. 1976
Green sunfish, Lepomis cyanellus	S	U	-	48	150,000	66,424	Sorensen, 1976a
Bluegill (juvenile), Lepomis macrochirus	FT	M	140-152	96	41,760	41,760	Cardwell, et al. 1976
Bluegill (fingerling), Lepomis macrochirus	S	U	29	48	290	128	Hughes & Davis, 1967
Bluegill, Lepomis macrochirus	S	U	52-53	96	15,370	8,403	Inglis & Davis, 1972
Bluegill, Lepomis macrochirus	S	U	209-210	96	16,240	8,878	Inglis & Davis, 1972

Table 1. (continued)

Organism	Bioassay Method*	Test Conc.**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (µg/l)	Adjusted LC50 (µg/l)***	Reference
✓ Bluegill, *Lepomis macrochirus*	S	U	365-368	96	15,486	8,466	Inglis & Davis, 1972

* S = static, FT = flow-through

** U = unmeasured, M = measured

*** All results expressed as arsenic; all tests were conducted with sodium arsenite except the one using the green sunfish and sodium arsenate.

Geometric mean of adjusted values = 17,239 µg/l $\frac{17,239}{3.9}$ = 4,400 µg/l

Lowest value from a flow-through test with measured concentration = 10,800 µg/l

Table 2. Freshwater invertebrate acute values for arsenic***

Organism	Bioassay Method*	Test Conc.**	Hardness (mg/l as $CaCO_3$)	Time (hrs)	LC50 (µg/l)	Adjusted LC50 (µg/l)	Reference
Cladoceran, *Daphnia magna*	S	U	45	48	7,400	6,268	Biesinger & Christensen, 1972
Cladoceran, *Daphnia magna*	S	U	-	48	5,278	4,470	Anderson, 1946
Cladoceran, *Daphnia pulex*	S	U	-	48	1,044	884	Sanders & Cope, 1966
Cladoceran, *Simocephalus serrulatus*	S	U	-	48	812	688	Sanders & Cope, 1966
Stonefly, *Pteronarcys californica*	S	U	-	96	22,040	18,668	Sanders & Cope, 1968

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* S = static

** U = unmeasured

*** All results expressed as arsenic; all tests were conducted with sodium arsenite except for the one by Biesinger and Christensen (1972) that used sodium arsenate.

Geometric mean of adjusted values = 2,784 µg/l $\frac{2,784}{21} = 130$ µg/l

Table 3. Freshwater invertebrate chronic values for arsenic** (Biesinger Christensen, 1972)

Organism	Test*	Limits (µg/l)	Chronic Value (µg/l)	Hardness (mg/l as $CaCO_3$)
Cladoceran, *Daphnia magna*	LC	520-1,400	853	45

* LC = life cycle or partial life cycle

** Result expressed as arsenic; test conducted with sodium arsenate

Geometric mean of chronic values = 853 µg/l $\frac{853}{5.1}$ = 170 µg/l

Lowest chronic value = 853 µg/l

Table 4. Freshwater plant effects for arsenic*

Organism	Effect	Hardness (mg/l as $CaCO_3$)	Concentration (ug/l)	Reference
Alga, *Cladophora* sp	100% kill in 2 wks	--	2,320	Cowell, 1965
Alga, *Pithophora* sp	Controlled	--	3,040	Lawrence, 1958
Alga, *Hydrodictyon* sp	Controlled	--	3,040	Lawrence, 1958
Alga, *Spirogyra* sp	100% kill in 2 wks	--	2,320	Cowell, 1965
Alga, *Zygnema* sp	100% kill in 2 wks	--	2,320	Cowell, 1965
Submerged plant, *Potamogeton* sp	95% kill in 1 mo	--	2,320	Cowell, 1965

* Results expressed as arsenic; all tests were conducted with sodium arsenite.

Lowest plant value = 2,320 µg/l

Table 5. Freshwater residues for arsenic

Organism	Bioconcentration Factor	Hardness (mg/l as $CaCO_3$)	Time (days)	Compound Tested	Reference
Cladoceran, *Daphnia magna*	10	42-45	21	Arsenic trioxide	Spehar, et al. (Manuscript)
Cladoceran, *Daphnia magna*	4	42-45	21	Arsenic pentoxide	Spehar, et al. (Manuscript)
Cladoceran, *Daphnia magna*	4	42-45	21	Disodium methyl arsenate	Spehar, et al. (Manuscript)
Cladoceran, *Daphnia magna*	5	42-45	21	Sodium dimethyl arsenate	Spehar, et al. (Manuscript)
Scud, *Gammarus pseudolimnaeus*	<1	42-45	28	Arsenic trioxide	Spehar, et al. (Manuscript)
Scud, *Gammarus pseudolimnaeus*	<1	42-45	28	Arsenic pentoxide	Spehar, et al. (Manuscript)
Scud, *Gammarus pseudolimnaeus*	<1	42-45	28	Disodium methyl arsenate	Spehar, et al. (Manuscript)
Scud, *Gammarus pseudolimnaeus*	<1	42-45	28	Sodium dimethyl arsenate	Spehar, et al. (Manuscript)
Snail, *Helisoma campanulata*	17	42-45	28	Arsenic trioxide	Spehar, et al. (Manuscript)
Snail, *Helisoma campanulata*	6	42-45	28	Arsenic pentoxide	Spehar, et al. (Manuscript)
Snail, *Helisoma campanulata*	4	42-45	28	Disodium methyl arsenate	Spehar, et al. (Manuscript)
Snail, *Helisoma campanulata*	5	42-45	28	Sodium dimethyl arsenate	Spehar, et al. (Manuscript)
Snail, *Stagnicola emarginata*	3	42-45	28	Arsenic trioxide	Spehar, et al. (Manuscript)
Snail, *Stagnicola emarginata*	3	42-45	28	Arsenic pentoxide	Spehar, et al. (Manuscript)
Snail, *Stagnicola emarginata*	3	42-45	28	Disodium methyl arsenate	Spehar, et al. (Manuscript)
Snail, *Stagnicola emarginata*	3	42-45	28	Sodium dimethyl arsenate	Spehar, et al. (Manuscript)

Table 5. (Continued)

Organism	Bioconcentration Factor	Hardness (mg/l as $CaCO_3$)	Time (days)	Compound Tested	Reference
Stonefly, *Pteronarcys dorsata*	9	45	28	Arsenic trioxide	Spehar, et al. (Manuscript)
Stonefly, *Pteronarcys dorsata*	7	45	28	Arsenic pentoxide	Spehar, et al. (Manuscript)
Stonefly, *Pteronarcys dorsata*	9	45	28	Disodium methyl arsenate	Spehar, et al. (Manuscript)
Stonefly, *Pteronarcys dorsata*	7	45	28	Sodium dimethyl arsenate	Spehar, et al. (Manuscript)
Rainbow trout, *Salmo gairdneri*	0	45	28	Arsenic trioxide	Spehar, et al. (Manuscript)
Rainbow trout, *Salmo gairdneri*	0	45	28	Arsenic pentoxide	Spehar, et al. (Manuscript)
Rainbow trout, *Salmo gairdneri*	0	45	28	Disodium methyl arsenate	Spehar, et al. (Manuscript)
Rainbow trout, *Salmo gairdneri*	0	45	28	Sodium dimethyl arsenate	Spehar, et al. (Manuscript)
Bluegill, *Lepomis macrochirus*	4	--	28	Arsenic trioxide	U.S. EPA, 1978

Geometric mean of all non-zero bioconcentration factors for all species = 5

Table 6. Other freshwater data for arsenic*

Organism	Test Duration	Effect	Hardness (mg/l as $CaCO_3$)	Result (µg/l)	Compound Tested	Reference
Cladoceran, (not specific)	4 mos	Significant population reduction in 1 wk	-	2,320	Sodium arsenite	Cowell, 1965
Cladoceran, *Daphnia magna*	3 wks	LC50	45	2,850	Sodium arsenate	Biesinger & Christensen, 1972
Cladoceran, *Daphnia magna*	26 hrs	LC50	-	3,770	Sodium arsenite	Crosby & Tucker, 1966
Cladoceran, (not specific)	16 wks	Reduced population	310	2,320	Sodium arsenite	Gilderhus, 1966
Copepod, (not specific)	16 wks	Reduced population	310	2,320	Sodium arsenite	Gilderhus, 1966
Copepod, (not specific)	4 mos	Reduced population in 1 wk	-	2,320	Sodium arsenite	Cowell, 1965
Rotifer, (not specific)	4 mos	Reduced population in 1 wk	-	2,320	Sodium arsenite	Cowell, 1965
Rotifer, (not specific)	16 wks	Reduced population	310	11,136	Sodium arsenite	Gilderhus, 1966
Shrimp, *Hyalella knickerbockeri*	5 days	30% survival	-	4,469	Arsenic trioxide	Surber & Meehean, 1931
Amphipod, *Gammarus pseudolimnaeus*	7 days	20% survival	-	961	Arsenic trioxide	Spehar et al., (Manuscript)
Mayfly (nymph), *Caenis diminuta*	5 days	75% survival	-	2,234	Arsenic trioxide	Surber & Meehean, 1931
Mayfly (nymph), *Caenis diminuta*	5 days	38% survival	-	5,958	Arsenic trioxide	Surber & Meehean, 1931
Mayfly (nymph), *Callibaetis sp*	5 days	5.8% survival	-	4,469	Arsenic trioxide	Surber & Meehean, 1931
Dragonfly (nymph), *Libellula satorata*	5 days	56% survival	-	10,640	Arsenic trioxide	Surber & Meehean, 1931

Table 6. (Continued)

Organism	Test Duration	Effect	Hardness (mg/l as $CaCO_3$)	Result (µg/l)	Compound Tested	Reference
Rainbow trout (juvenile), Salmo gairdneri	21 days	Decrease in fat weight gain	127	1,000	Arsenic trioxide	Speyer, 1974; Speyer & Leduc, 1975
Brook trout, Salvelinus fontinalis	262 hrs	LC50	140-152	10,440	Sodium arsenite	Cardwell, et al. 1976
Goldfish (juvenile), Carassius auratus	336 hrs	LC50	140-152	18,618	Sodium arsenite	Cardwell, et al. 1976
Fathead minnow (juvenile), Pimephales promelas	336 hrs	LC50	140-152	10,556	Sodium arsenite	Cardwell, et al. 1976
Green sunfish, Lepomis cyanellus	3 wks	Ultrastructural changes in liver	92	31,700	Sodium arsenate	Sorensen, 1976b
Green sunfish, Lepomis cyanellus	678 hrs	LT50 at 10° C	92	60,000	Sodium arsenate	Sorensen, 1976c
Green sunfish, Lepomis cyanellus	210 hrs	LT50 at 20° C	92	60,000	Sodium arsenate	Sorensen, 1976c
Green sunfish, Lepomis cyanellus	124 hrs	LT50 at 30° C	92	60,000	Sodium arsenate	Sorensen, 1976c
Green sunfish, Lepomis cyanellus	527 hrs	LT50 at 20° C	92	30,000	Sodium arsenate	Sorensen, 1976c
Green sunfish, Lepomis cyanellus	209 hrs	LT50 at 30° C	92	30,000	Sodium arsenate	Sorensen, 1976c
Bluegill (juvenile), Lepomis macrochirus	16 wks	Reduced survival and growth	310	2,320	Sodium arsenite	Gilderhus, 1966
Bluegill (adult), Lepomis macrochirus	16 wks	Histopathological alterations	310	11,136	Sodium arsenite	Gilderhus, 1966
Bluegill, Lepomis macrochirus	5 mos	Reduction in fish numbers	-	3,040	Sodium arsenite	Lawrence, 1958

* Results expressed as arsenic

SALTWATER ORGANISMS

Introduction

The arsenic data base for saltwater organisms is inadequate to assess comparative sensitivity among a variety of species and their life stages or importance of water quality parameters such as salinity to arsenic toxicity. In addition, these data do not distinguish differences, if any, between various oxidation states. Arsenic toxicity values are expressed herein as arsenic.

Acute Toxicity

Acute toxicity data representative of arsenic and saltwater aquatic life are limited to evaluations of one fish and two invertebrate species. Alderdice and Brett (1957) assessed toxicity of arsenic to chum salmon using a flow-through test with unmeasured concentrations to determine a 48-hour LC50 of 8,331 µg/l. Adjustment for exposure method, time and unmeasured concentration gives an LC50 of 5,196 µg/l. The geometric mean, divided by the sensitivity factor, results in the Final Fish Acute Value of 1,400 µg/l (Table 7).

Nelson, et al. (1976) employed a renewal test to determine arsenic toxicity to juvenile bay scallop, and Calabrese, et al. (1973) evaluated toxicity to American oyster embryos using a static test. Toxicity from these tests with unmeasured concentrations defined a 96-hour LC50 of 3,490 µg/l for bay scallops and a 48-hour LC50 of 4,325 µg/l for American oyster embryos (Table 8). After adjustment for test method, time and unmeasured arsenic concentration the geometric mean was calculated to be 3,291 µg/l.

The geometric mean divided by a sensitivity factor of 49 provides a Final Invertebrate Acute Value of 67 µg/l which concentration also becomes the Final Acute Value since it is lower than the equivalent value for fish.

Chronic Toxicity

No data are available on the chronic toxicity of arsenic to saltwater fish or invertebrate species.

Plant Effects

Saltwater plant data for arsenic are limited to developmental data on the sporelings of a red alga resulting in a Final Plant Value of 580 µg/l (Table 9).

Residues

The bioconcentration factor for the bay scallop is 15 (Table 10), but, since no maximum permissible tissue concentration is available, no Residue Limited Toxicant Concentration can be calculated.

Miscellaneous

No other data from Table 11 suggest any more sensitive effects for fish or invertebrate species than the acute toxicity data reported (Tables 7 and 8).

CRITERION FORMULATION

Saltwater - Aquatic Life

Summary of Available Data

The concentrations below have been rounded to two significant figures. All concentrations herein are expressed in terms of arsenic.

Final Fish Acute Value = 1,400 μg/l

Final Invertebrate Acute Value = 67 μg/l

Final Acute Value = 67 μg/l

Final Fish Chronic Value = not available

Final Invertebrate Chronic Value = not available

Final Plant Value = 580 μg/l

Residue Limited Toxicant Concentration = not available

Final Chronic Value = 580 μg/l

0.44 x Final Acute Value = 29 μg/l

No saltwater criterion can be derived for arsenic using the Guidelines because no Final Chronic Value for either fish or invertebrate species or a good substitute for either value is available. Data for arsenic and freshwater organisms can be used to estimate a criterion.

For arsenic and freshwater organisms, 0.44 times the Final Acute Value is less than the Final Chronic Value derived from results of a life cycle test with Daphnia magna. Therefore, a reasonable estimate of a criterion for arsenic and saltwater organisms would be 0.44 times the Final Acute Value.

The maximum concentration for arsenic is the Final Acute Value of 67 μg/l and the estimated 24-hour average concentration is 0.44 times the Final Acute Value. No important adverse effects on saltwater aquatic organisms have been reported to be caused by concentrations lower than the 24-hour average concentration.

CRITERION: For arsenic the criterion to protect saltwater aquatic life as derived using procedures other than the Guidelines is 29 μg/l as a 24-hour average and the concentration should not exceed 67 μg/l at any time.

Table 7. Marine fish acute values for arsenic***(Alderdice & Brett, 1957)

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (µg/l)	Adjusted LC50 (µg/l)
Chum salmon, *Onchorhynchus keta*	FT	U	48	8,331	5,196

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* FT = flow-through

** U = unmeasured

***All results expressed as arsenic; test was conducted with arsenic trioxide.

Geometric mean of adjusted values = 5,196 µg/l $\frac{5,196}{3.7}$ = 1,400 µg/l

Table 8. Marine invertebrate acute values for arsenic***

Organism	Bioassay Method*	Test Conc.**	Time (hrs)	LC50 (ug/l)	Adjusted LC50 (ug/l)	Reference
Bay scallop (juvenile), Argopecten irradians	R	U	96	3,490	2,956	Nelson, et al. 1976
American oyster (embryo), Crassostrea virginica	S	U	48	4,330	3,668	Calabrese, et al. 1973

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* S = static, R = renewal

** U = unmeasured

***All results expressed as arsenic; both tests were conducted with sodium arsenite.

Geometric mean of adjusted values = 3,293 µg/l $\frac{3,293}{49}$ = 67 µg/l

Table 9. Marine plant effects for arsenic* (Boney, et al. 1959)

Organism	Effect	Concentration (µg/l)
Red alga, *Plumaria elegans*	Arrested development of sporelings	577

Lowest plant value = 577 µg/l

* All results expressed as arsenics; test was conducted with sodium arsenite.

Table 10. Marine residues for arsenic* (Nelson, et al. 1976)

Organism	Bioconcentration Factor	Time (days)
Bay scallop (juvenile), *Argopecten irradians*	15	4

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* All results expressed as arsenic; test was conducted with sodium arsenite.

Table 11. Other marine data for arsenic

Organism	Test Duration	Effect	Result (ug/l)	Reference
Pink salmon, *Onchorhynchus gorbuscha*	96 hrs	LC100	12,307	Holland, et al. 1960
Pink salmon, *Onchorhynchus gorbuscha*	7 days	LC100	7,195	Holland, et al. 1960
Pink salmon, *Onchorhynchus gorbuscha*	10 days	LC54	3,787	Holland, et al. 1960
Polychaete worm, *Nereis diversicolor*	192 hrs	LC50	>25,000*	Bryan, 1976

Lowest value = 3,787 μg/l

* Data not presented as arsenic ion

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Mammalian Toxicology and Human Health Effects

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EXPOSURE

Water. In an U. S. Environmental Protection Agency national study of residential tap water, 66.8% of the one time grab samples collected from 3834 residences had arsenic levels greater than 0.1 μg/liter. The average, minimum, and maximum levels of the samples with detectable arsenic were 2.37, 0.50, and 213.6 μg/liter, respectively (Greathouse and Craun, 1978; Greathouse, statistician - EPA, unpub.). In 1975 it was reported that 5 out of 566 samples collected from Interstate Carrier Water Supplies exceeded 10 μg/liter and that the maximum level was 60 μg/liter (U.S. Environmental Protection Agency, 1975). Well water samples collected during 1976 at 59 residences in a Fairbanks, Alaska suburban community had a mean arsenic content of 224 μg/liter with a range from 1.0 to 2,450 μg/liter (Public Health Service, 1977). Moderately elevated levels of arsenic, 10 to 330 μg/liter, are present in potable waters of some smaller communities in Utah, Nevada, and California (Valentine, project director - UCLA, personal communication).

There have been a number of other reports of isolated instances of higher than usual concentration of arsenic in well waters. Goldsmith, et al. (1972) reported on a study, in Lassen County, California, of the health effects associated with drinking well waters with arsenic levels ranging from 100 μg/l or less to 1400 μg/l. In Perham, Minnesota, a newly bored well was associated with illness in 13 people whose hair samples contained arsenic at 37-1,680 μg/g. The well water serving these patients contained arsenic from 11,800 to 21,000 μg/liter; this was later determined to come from ground contamination by residual arsenical grasshopper bait (Feinglass, 1973). Forty-five out of 558 water samples collected from Lane County, Oregon had arsenic values greater than 50 µg/liter. The mean, maximum and miniumum values detected were 9.6, 2,150, and 0 µg/liter, respectively (Morton et al. 1976).

Much information has been collected concerning the levels of arsenic in fresh surface waters (Table 1). Arsenic occurrence is very widespread and even occurs in some rain water. Most of the high values reported in rivers and lakes are probably due to industrial contamination (The National Research Council, 1977a). Angino, et al. (1970) have shown that household detergents (mostly of the high-phosphate type) widely used in the United States contained arsenic at 1-73 µg/g; their use probably contributes significant amounts of arsenic to surface sources. Sollins (1970), however, felt that, after dilution during use, the concentration would be well below the recommended maximum and constitute no particular hazard. It has been generally assumed that surface waters, like the ocean, are "self-purifying" with respect to arsenic - i.e., that the arsenic is removed from solution by deposition with sediments; but quantitative studies are lacking. Sediments are always higher in arsenic than the waters with which they are associated (The National Research Council, 1977a).

Food. A 1966 food survey found arsenic in 3.2% of the samples at a range of 0.10 to 4.7 µg/g (Cummings, 1966). In a 1967 market-basket survey, arsenic was present in 10% of the composite samples (Duggan and Lipscomb, 1969). In 1968, arsenic occurred in 18% of the samples. Whether the arsenic occurred naturally or as a result of man's activities was not known.

Schroeder and Balassa (1966) sampled foods and beverages from American chain stores (Table 2). Fish and Seafoods contained the most arsenic (mean of 4.64 µg/g) and fruits contained the least (mean of 0.17 µg/g). Generally, the only foods which are high in arsenic are seafoods. Chapman (1926) found that mussels, oysters, and scallops contained very high levels of arsenic (means of up to 80 µg/g). In comparison, mixed freshwater fish contained a mean of 0.65 µg/g arsenic. Zook, et al. 1976 reported that in a survey of selected seafoods for metal content, the overall arsenic mean content was 2.6 µg/g. The lowest mean arsenic value was found in wild catfish - 0.1 µg/g. Thus, arsenic appears to be present in small amounts in nearly all foods, with marine invertebrates containing the highest arsenic levels.

A bioconcentration factor (BCF) relates the concentration of a chemical in water to the concentration in aquatic organisms. Since BCF's are not available for the edible portions of all four major groups of aquatic organisms consumed in the United States, some have to be estimated. A recent survey on fish and shellfish consumption in the United States (Cordle, et al. 1978) found that the per capita consumption is 18.7 g/day. From the data on the nineteen major species identified in the survey, the relative consumption of the four major groups can be calculated.

Tests on the bioconcentration of a variety of arsenic compounds resulted in BCF values from zero to four for freshwater fish (Spehar, et al. Manuscript; U.S. EPA, 1978). These were all based on whole body measurements. Based on data for lead and cadmium, arsenic would probably have a lower BCF for fish and decapod muscle than for fish whole body. A BCF of 15 was obtained for arsenic using the bay scallop (Nelson, et al. 1976).

Group	Consumption (Percent)	Bioconcentration factor
Freshwater fishes	12	1
Saltwater fishes	61	1
Saltwater molluscs	9	15
Saltwater decapods	18	1

Using the data for consumption and bioconcentration for each of these groups, the weighted average BCF for arsenic is 2.3 in consumed fish and shellfish.

Crecelius (1977a) has analyzed 19 samples of domestic table wines for several species of arsenic; 13 varieties of white and red wines were included. The ranges of concentrations were < 1-420 µg/l, < 1-110 µg/l, and 1-530 µg/l for arsenite, arsenate, and total arsenic respectively; mean levels were 127, 32, and 153 µg/l respectively. Clearly the majority of the arsenic was present as arsenite. Both dimethylarsinic acid and methylarsonic were below the detection limit of 1 µg/l in these wine samples.

In 1966 Schroeder and Balassa (1966) estimated that the average daily diet contains 900 μg of arsenic. This estimate was based on the results of arsenic determinations for meats, sea food, and vegetables purchased from Vermont chain stores. Arsenic in an institutional diet was estimated to be 400 μg per day. One reason for this lower level is that the institutional diet did not contain any seafood. The World Health Organization reported that arsenic intakes vary from 7 to 60 μg per day (The National Research Council, 1977a). Jelinek and Corneluissen (1977) report that the Food and Drug Administration (FDA) has monitored for arsenic in its Total Diet Survey since inception of the program. The data from this program indicated that the average daily intake for arsenic trioxide has decreased from about 130 μg/day in 1968 to about 20 μg/day in 1974. It is likely that the differences among the estimates of total daily intake are partially due to variations in the species of arsenic considered.

Drugs. Arsenic was known as a therapeutic agent to the ancient Greeks and Romans. The introduction of Salvarsan (arsphenamine) by Ehrlich at the turn of the century gave rise to intense activity on the part of the organic chemists and its estimated that more than 32,000 arsenic compounds were synthesized (The National Research Council, 1977a).

The advent of penicillin disposed of antiluetic arsenicals, and other newer drugs have nearly eliminated the use of other organic arsenicals. In current human therapeutics, arsenicals are of importance only in the treatment of certain tropical diseases (Harvey, 1975).

Inhalation. Suta (1978) has evaluated atmospheric arsenic concentration data for 1974 for 267 locations representing a resident population of more than 58,000,000 people; none of the major man-made sources of atmospheric as(nonferrous smelters, pesticide manufactures, coal fired power plants, glass cotton gins) are present in any of the locations. The annual average concentrations for all sites ranged from below the detection limit to 83 ng/m^3. The mean of the annual average concentrations for all locations was 3 ng/m^3. The average concentration for eight locations near nonferrous smelters was 30 ng/m^3, and the average concentration for eight locations in remote rural areas was 0.4 ng/m^3 assuming a concentration of zero for samples reported as below detection limit. The lower detection limit for an individual arsenic sample is 1 ng/m^3 (Suta, 1978).

Suta (1978) has estimated air arsenic concentrations and exposed population numbers associated with major man-made sources of arsenic in the atmosphere (Table 4). He states that due to the paucity of relevant data and information, the large number of required assumptions, and the inherent inaccuracies of the modeling approach, the accuracy of these exposure estimates can not be judged quantitatively. It should be noted that the exposure concentrations shown in the table are annual averages. Exposures for selected times may be much higher or lower than the annual averages. Population exposures for concentrations below 3 ng/m^3 are not given because they are assumed to equal the average urban background concentration. Population exposures are not given for concentrations below 10 ng/m^3 for some copper smelter alternative estimates because to do so would have required extrapolation of modeling results beyond 20 km for the source. At these greater distances, the accuracy of the modeling results became increasingly uncertain.

It is quite apparent from these qualified estimates that in some areas of the country, the general population is exposed to high levels of atmospheric arsenic when compared to ambient levels in uncontaminated areas. Klemmer, et al, 1975 analyzed 61 samples of dusts collected from Hawaii homes for arsenic content and found that the levels range from 3 to 1080 µg/g. Since house dust has been implicated as a significant source of human pesticide burden, it may also be a significant source of arsenic exposure in some homes.

Dermal. No information was found concerning the levels and/or duration of dermal exposure to arsenic. Since arsenic compounds are used in insecticides, herbicides, fungicides, algicides, sheepdigs, wood preservatives, and dyestuffs and for the eradication of tapeworm in sheep and cattle (The National Research Council, 1977a), it seems likely that the dermal route may be a source of arsenic exposure for some segments of the population.

PHARMACOKINETICS

Absorption. The main routes by which arsenic can enter the body are inhalation and ingestion, although absorption through the skin is also a possible minor route of entry (Sollman, 1964; Oehme, 1972; Garb and Hine, 1977). The biological fate of an inhaled particle is dependent on particle size. The optimum range for deposition in the lower tracheobronchial tree, where it can either lodge or be absorbed into the blood stream, is 0.1 to 2 µm. Particles smaller than 0.1 um do not come out of suspension in the inhaled air and are exhaled. Particles larger than 2 um are trapped by the mucous membranes of the nose and throat and are swallowed; these enter the gastrointestinal tract, either to be absorbed or to be excreted (Falk and Kotin, 1961).

Emissions of arsenic and other toxic trace elements from high-temperature combustion sources such as smelters have been observed to be mainly in the size range of less than 1 um in diameter. Thus they are respirable and are capable of being absorbed through the lungs, the most efficient route of entry (Natusch, et al. 1974).

Human inhalation studies provide valuable data on arsenical uptake, absorption, and excretion. Eleven volunteers with terminal lung cancer inhaled arsenic-74; eight inhaled smoke from a cigarette impregnated with sodium arsenite solution and three inhaled arsenite in an aerosol solution (Holland et al. 1959). Lungs of the subjects who inhaled arsenic-laden cigarette smoke absorbed from 4.8% to 8.8% of the total radioactivity, whereas 32% and 62% of the aerosol arsenic solution were absorbed by the lungs of two subjects. The percentage of arsenic absorbed by the lungs of the third subject was not given. Arsenic content in the respiratory tract decreased rapidly during the first few days and leveled off to 20% to 30% of the original uptake in about 4 days.

Water soluable arsenicals are readily absorbed through the gastrointestinal tract; some nonpolar organic forms are also absorbed from the intestine (Hwang and Schanker, 1973; Tarrant and Allard, 1972). Arsenic trioxide is only slightly soluable in water and is not well absorbed. Pentavalent arsenic, whether inorganic or organic, is better absorbed than the trivalent form, because pentavalent is less reactive with membranes of the gastrointestinal tract. Arsenites are generally better absorbed through skin than arsenates, and absorption depends heavily on lipid solubility of the compound (The National Research Council, 1977b).

Stokinger and Woodward (1957) have estimated that 80% of ingested inorganic arsenic is absorbed versus 20% of inhaled arsenic.

Distribution. After absorption by the lungs or the alimentary tract, arsenic is transported via the blood to other parts of the body. Hunter et al. (1942) studied the distribution of radioactive arsenical compounds after oral and parenteral administration and found arsenic in the liver, kidney, lungs, spleen, and skin during the first 24 hours after administration. Arsenic concentration in the skin increased for several days after 24 hours.

Small concentrations were found in the brain, heart, and uterus. Bone and muscle concentrations of arsenic were low, but the overall amounts of arsenic in these tissues may be high due to their mass. In conjunction with the skin, they comprise the major deports of arsenic in the body. Vallee, et al. (1960) noted that small quantities of arsenic, even when the dose is low, may be detected in tissues of ectodermal origin such as the hair and nails many months after it has disappeared from the urine and feces.

Inorganic arsenic does not cross the blood-brain barrier in humans, although it may do so in some anthropoids (Vallee, et al. 1960). In man and rats, arsenic is transferred across the placenta (Vallee, et al. 1960). In radioactive tracer studies on arsenic in rats, 95% to 99% of the arsenic in the whole blood was detected in erythrocytes whereas in humans, monkeys and rabbits, arsenic was more equally distributed between blood cells and plasma proteins. The form of the arsenic administered, arsenate or arsenite, played a role in this distribution (Hunter, et al. 1942; Hogan and Eagle, 1944; Mealy, et al. 1959). In various mammalian tissue fractions, the greater part of the injected radio-arsenic is found in the protein fractions; small amounts are present in the acid-soluble portions of the tissue, and insignificant amounts are found in lipids. The nucleoproteins do not take up more arsenic than other proteins (Lowry, et al. 1942). The major carriers of arsenic in the plasma of mice are alpha-1 globulins. In each organ or tissue, it is known that arsenic can chemically combine with sulfhydryl groups (Vallee, et al. 1960, Subcommittee on Toxicology of Metals, 1977).

Accumulation and biological half-time. Bencko and Symon (1970) administered arsenic trioxide by inhalation or drinking water to animals and found that arsenic accumulation was biphasic and that it did not have the character of a simple saturation curve. In the first phase, the arsenic concentration increased in all organs and tissues which were investigated, and in the second phase it decreased. They concluded that the decrease of arsenic concentrations in internal organs, for example, the liver, was probably dependent on the activation or enhancement of an arsenical excretion mechanism.

About 80% of the absorbed arsenic is retained and widely distributed in tissues, such as the liver, kidney, spleen, bone marrow, skin, and the hair and nails. The biological half-times in the blood of chickens given a single oral dose of arsanilic acid or sodium arsenate were 36 hours and 60 hours respectively (Overby and Fredrickson, 1963).

Crecelius (1975, 1977b) has reported biological half-times of 10 hours for arsenite and 30 hours for methylated forms of arsenic in a person who drank wine containing arsenite.

Metabolism. Little information is available on the changes in the chemical forms of arsenic that occur within the body (Crecelius, 1977b). However, reviews and summaries on the biochemistry of arsenic in man indicate that (1) arsenic which enters the blood stream is excreted mainly in the urine; (2) arsenic has a biological half life of 30-60 hours; and (3) arsenic is excreted in urine in several forms, including arsenite, arsenate, methylarsonic acid, dimethylarsinic acid, and other organically bound arsenic compounds (Vallee, et al. 1960; Buchanan, 1962; Schroeder and Balassa, 1966; Frost, 1976; Lisella, et al. 1972; Valee, 1973; Peoples, 1975).

Excretion. Arsenic is excreted mainly in urine, to some extent in the feces (Hunter, et al. 1942) and through normal hair loss and skin shedding. The available evidence indicates that ingested inorganic arsenate is excreted from the body mainly in the pentavalent form but some percentage may be reduced (Lanz,et al. 1950; Ginsburg and Lotspeich, 1963; Ginsburg, 1965). Trivalent arsenic appears to be primarily methylated *in vivo* to methylarsonic acid and dimethylarsinic acid (Braman and Foreback, 1973; Crecelius, 1975, 1977b) Urinary excretions of methylated arsenic following exposure to airborne arsenic has been recently reported (Smith et al. 1977).

EFFECTS

Toxicity. The predominant manifestations of arsenic poisoning due to ingestion are gastrointestinal disturbances (Dreisbach, 1971). The intensity and onset of symptoms are determined to some extent by the physical form of the arsenical, quantity ingested, and whether of not a meal has been recently eaten. Hemolysis is the primary manifestation of arsine poisoning.

The first symptom of acute poisoning is a feeling of throat constriction followed by difficulty in swallowing, epigastric discomfort, and violent abdominal pain accompanied by vomiting and a watery diarrhea (Buchanan, 1962). Intense thirst is usually present (Rentoul and Smith, 1973). Cramps may be present in muscles at the lower limbs. Death, which is generally preceded by restlessness, couvulsions, or coma, may result from cardiac failure. In subacute poisoning, symptoms are less intense. If death is not immediate, jaundice and oliguria or anuria occur after 1 to 3 days (Dreisbach, 1971). The toxic action of arsenic on the gut lining epithelium is seen microscopically as a cloudy swelling and fatty infiltration (Buchanan, 1962). In less severe cases of occasional occupational exposure, recovery usually occurs and may either be complete or be followed by symptoms characteristic of chronic poisoning.

The acute oral toxicity of arsenic trioxide using commercial grade (97.7% As_2O_3 with 1.18% Sb_2O_3) and highly purified arsenic trioxide (99.99% As_2O_3) was tested in mice and rats by Harrison,et al. (1958). Test solutions were administered intraesophageally. For Webster Swiss mice, acute oral LD_{50} was estimated as 39.9 mg arsenic per kilogram body weight for purified As_2O_3 and 42.9 mg arsenic per kilogram body weight for the commerical grade. The LD_{50} for Sprague Dawley albino rats was 15.1 mg arsenic per kilogram for the pure As_2O_3 and 23.6 mg arsenic per kilogram for the crude form. While the LD_{50} for the purified arsenic was lower in both species, the purified arsenic was a less severe gastrointestinal irritant than the commercial form of arsenic trioxide. Retching and gastrointestinal damage were attributed to the presence of antimony in the unpurified preparation.

Several reports of acute arsenical poisoning by ingestion have been cited in the literature. An acute poisoning epidsode occurred in two Indonesian orphanages from the ingestion of arsenic-contaminated rice which was prepared independently in each orphanage (Tjaij and Aziz, 1971). Laboratory analyses showed small amounts of arsenic in the urine of five children and in the vomit of one child. Symptoms of vomiting, abdominal pain, diarrhea, lassitude, dizziness, and headache appeared in 109 children and 48 adults 1 to 2 hours after ingestion of the rice. Nine children were hospitalized; all victims fully recovered.

Systemic exposure to amounts of arsenic sufficient to cause symptoms but inadequate to produce systemic collapse is of particular interest. The patient may go for weeks with gradually increasing or variable signs and symptoms related to several organ systems and giving the appearance of a progressive chronic disease state. If death occurs, it may appear to have been the consequence of the inexorable course of an obscure "natural" disease. This appearance has contributed to the popularity of arsenic as an agent of homicide (The National Research Council, 1977a).

The method of arriving at a therapeutic dose of Fowler's solution was based on finding the patient's tolerance to increasing but nontoxic doses. As described by Holland (1904) the patient was given 5 drops (about 9 mg of arsenic trioxide, or 6.8 mg of arsenic) "well diluted, after meals (i.e., three times a day), increasing the dose one drop daily until the disease is under control or until the eyelids puff and the bowels move too freely. . . The dose is then reduced to a safer quantity, and continued until the warning returns, when it is again reduced. . . For some persons even the minimum dose will produce unpleasant effects; one case of erythroderma has been reported after a patient received 10 mg of arsenic trioxide (7.6 mg of arsenic) taken over a 2-day period (The National Research Council, 1977a)."

Holland (1904) used the information gained from personal observation and reports of suicides and criminal cases which used rat or fly poison, as well as Fowler's solution, to describe the effects of arsenic poisoning. Occasionally, enthusiastic patients would overdo their use of medicinal arsenic, but this was uncommon, because of the associated discomfort. Holland described subacute poisoning as producing loss of appetite, fainting, nausea and some vomiting, dry throat, shooting pains, diarrhea, nervous weakness, tingling of the hands and feet, jaundice, and erythema. Longer exposure resulted in dry, falling hair; brittle, loose nails; eczema; darker skin; exfoliation; and a horny condition of the palms and soles.

Mizuta, et al. (1956) reported on 220 patients of all ages who had been poisoned by contaminated soy sauce, with an average estimated ingestion of roughly 3 mg of arsenic (probably as calcium arsenate) daily for 2-3 weeks. In this group, 85% had facial edema and anorexia; fewer than 10% had exanthemata, desquamation, and hyperpigmentation; and about 20% had peripheral neuropathy. Except for headaches and fever, the findings in these patients appeared to be very similar to those reported by Reynolds (1901). Although the majority of patients' livers were enlarged, relatively few abnormalities were found in liver-function tests; and the histopathologic description of five liver biopsies did not reveal severe degenerative changes. There were no findings suggestive of congestive failure, but electrocardiograms were abnormal in 16 of 20 patients, and this confirmed the reports of Josephson et al. (1951) and Nagai, et al. (1956). The Japanese patients' symptoms tended to diminish after 5 or 6 days, despite continued intake of arsenic, and neurologic symptoms became prominent as much as 2 weeks after arsenic ingestion was discontinued, at which time urinary arsenic content remained high. Hair was found to contain arsenic at 2.8-13.0 µg/g near the root, compared with 0-1.5 µg/g near the end and 0.4-2.8 µg/g in hair from control patients.

In the early 1960's, physicians in Antofagasta, Chile, noted dermatologic manifestations and some deaths, particularly among children, that were traced to a water supply containing 800 µg/liter of arsenic. This water supply had been in operation only since 1958. Borgono and Greiber (1972) have reported on studies of the inhabitants of this city. They compared 180 inhabitants of Antofagasta with 98 people who lived in a city (Iquique, Chile) with a normal water supply. Most of the people studied were less than 10 years old. Among the residents of Antofagasta the primary symptoms reported were abnormal skin pigmentation (80%); chronic coryza (60%); hyperkeratosis (36%); various cardiovascular manifestations, i.e., Raynaud's syndrome (30%); acrocyanosis (27%); abdominal pain (39%); chronic diarrhea (7%); and lip herpes (13%). The incidence of these symptoms in the control population was substantially lower or nonexistent.

Two additional reports on the Antofagasta studies are worthy of note. Zaldivar (1974) further described a study on a total of 457 patients (208 males, 249 females) bearing cutaneous lesions (leukoderma, melanoderma, hyperkeratosis, squamous-cell carcinoma). Children (0-15 years of age) accounted for 69.2% of male cases, and for 77.5% of female cases. These patients exhibited high arsenic content in the hair. The mean concentration

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of arsenic in drinking water in the period 1968-1969 was 580 µg/g versus 80 µg/g in 1971, differing by a factor of 7.2. Such difference was attributed to a new filter plant, which started operation in May 1970. The average incidence rates per 100,000 population for cases with cutaneous lesions in 1968-1969 were 145.5 for males and 160.0 for females. The incidence rates decreased in 1971 to 9.1 for males and 10.0 for females.

Among the 337 registered children, 5 died showing thrombosis of brain arteries, thrombosis of mesenteric artery, restriction of lumen of coronary arteries, and/or myocardial infarction. Of the 64 registered adult males, 2 developed multiple skin carcinomata with lymph node metastases.

A number of questions are raised regarding this report. For example, the decrease in cutaneous lesions seemed to be too rapid, following installation of the water-treatment plant, suggesting other factors were involved. Protection of the 8-10-year-old age group showed up in three years and adults exposed for more than 15 years also had a decrease in incidence rate of cutaneous lesions.

In a follow-up study, Borgono, et al. (1976) investigated clinical and epidemiologic aspects of the cases first reported in 1971. Arsenic content in hair and nail clipping samples of the inhabitants of Antofagasta were determined and compared to the levels measured in the initial study reported in 1971. Similar measurements and comparisons were performed for cultivated vegetables and carbonated beverages. Also a clinical study was made in school children, looking for cutaneous lesions attributed to arsenicism. Six years after the water treatment plant started to operate the problem had diminished considerably. Arsenic determination of hair and nails of children 6 years of age or less, born since the water treatment plant went into operation, indicated no cutaneous lesions in this age group. However, those over 6 years of age still had significant arsenic residues in hair and nails. Although the clinical manifestations have improved, arsenic content of water, soft drinks, and in some foods are still considerably above safe levels and require additional sanitary engineering improvements.

Tseng, et al. (1968) surveyed a group of 40,421 residents of the southwest coast of Taiwan (from a population "at risk" of 103,154) and found that they suffered from a number of dermatologic and peripheral vascular problems. The overall male and female prevalence rates for the clinical findings are as follows: Hyperpigmentation 18.4 - 19.2%, 17.6%; Keratotic lesions 7.1 - 7.5%, 6.8%; and Blackfoot disease 0.9 - 1.2%, 0.7% for males and females respectively. The reason for the range of values for males was not explained. Skin cancer prevalence rates corresponded directly to age and arsenic exposure gradients (Table 9)(Tseng, 1977). The concentration of arsenic in the wells ranged from 17 to 1097 µg/l. No cases of melanosis or keratosis were found in a group of 2,552 people living in an area where the wells contained almost no arsenic.

There are many scattered case reports of subacute to chronic arsenic poisoning in the literature. Silver and Waixman (1952) described a patient who ingested approximately 8.8 mg of arsenic trioxide as Fowler's solution daily for a total period of 28 months, as a remedy for asthma. Signs of arsenic poisoning, manifested as increased freckling and as darkening of the nipples, first appeared in association with gastrointestinal symptoms after 13 months; redness and puffiness about the eyes and hyperkeratoses developed at approximately 1.5 years. Neurologic symptoms in the form of paresthesias and weakness were the last to be noted, occurring after 2 years. When the arsenic intake was stopped, the pigmentation lightened, but the hyperkeratoses remained, and the asthma became more difficult to control.

Perry, et al. (1948) noted that all of a group of chemical workers handling inorganic arsenic compounds had pigmentary changes and that one-third of them had "warts," although these were not well described. They reported that the cutaneous "changes were so evident that (the examiner) could readily tell whether the man . . . was a chemical worker." All these workers had increased urinary arsenic compatible in degree with the extent of exposure; this indicates systemic absorption of the arsenic from dust, probably through the lungs and skin. High-exposure areas of the plant had arsenic concentrations ranging from about 250 to 700 $\mu g/m^3$. The relationship of urine and hair arsenic to the prevalence of pigmentation and warts is shown in Table (5).

Holmqvist (1951) reported eczematous and follicular dermatitis in smelter workers, primarily on exposed skin. Patch tests showed sensitivity to both trivalent and pentavalent arsenic. Birmingham, et al. (1965) reported similar lesions that developed with a few months of the startup of a gold smelter that handled ores containing large amounts of arsenic sulfide. Dermatitis developed in half the mill workers and in 32 or 40 students in a nearby elementary school.

Butzengeiger (1940) reported that, of 180 vinedressers and cellarmen with symptoms of chronic arsenic poisoning, about 23% had evidence of vascular disorders of the extremities. Arsenical insecticides were used in the vineyards, and exposure occurred not only with spraying, but during work in the vineyards by inhalation of contaminated dusts and plant debris. Most of the workers consumed 1-2 liters of wine per day, and it was also believed to be contaminated with arsenic. All 15 workers with vascular disorders had hyperpigmentation, and all but two had palmar and plantar keratosis; six of the 15 had gangrene of the fingers and toes. The same association of vascular disorders, hyperpigmentation, and keratosis was observed in Taiwan (Yeh, 1963). Urinary arsenic content average 0.324 mg/liter, and hair arsenic, 0.39 ug/g. Butzengeiger (1949) reported that the electrocardiograms of 36 of 192 vinegrowers with chronic arsenic intoxication were definitely abnormal, with no other evident cause. The abnormalities included prolongation of the Q-T interval and a flattened T wave. In treated cases, these abnormalities diminished with the other evidence of toxicity. Similiar findings were reported by Barry and Herndon (1962) and Glazener, et al. (1968).

Fierz (1965) examined 262 patients who had received long courses of medicinal arsenic 6-26 years previously and found karatoses in 40% and typical skin cancer in 8%. There was evidence of a dose relationship for both keratoses and skin cancer. Patients who had received more than 400 ml of Fowler's solution (4 g of arsenic trioxide) had an incidence of hyperkeratoses of greater than 50%, but as little as 60 ml (600 mg of arsenic trioxide) had resulted in keratotic changes in one patient. As little as 75 ml (750 mg of arsenic trioxide) had been consumed by one patient with skin cancer. The shortest time to cancerous change was 6 years, with an average of 14 years, compared with Neubauer's estimate of 18 years (Neubauer, 1947). Fierz (1965) noted that 1,450 invitations for a free examination had been sent to patients who had been given the therapeutic arsenic. Beside the 262 who came for examination, 100 patients provided written reports, and information was obtained about the deaths of 11. Five of the 11 deaths were due to systemic cancer, and three to lung cancer. Sixteen of the 21 patients with cancer had typical keratoses, (Fierz, 1965).

Arguello, et al. (1938) reported on a large group of patients seen for arsenical skin cancers in the Cordoba region in Argentina, which had a high arsenic content in the drinking water (Bergoglio, 1964) and found keratoderma in "100% of our patients." Most patients also had associated hyperhidrosis and abnormalities of pigmentation, whereas those reported by Fierz (1965) did not. Arguello, et al. (1938) noted that the pigmentation appeared early and was variable among the patients. It was described as small dark spots 1-10 mm in diameter, with a tendency to coalesce, and appearing predominantly on the trunk, that is, in the areas not exposed to the sun. These and other authors have noted that atrophy may be associated with telangiectasia and loss of color, or leukoderma, between the hyperpigmented areas (the "raindrop" appearance cited by Reynolds (1901)).

The characteristics of the skin malignancies found in chronic arsenism have been reviewed by Yeh (1963) and Yeh, et al. (1968) in their reports on the Taiwan cases. A prominent, even necessary, clinical feature of arsenical skin cancer is its association with the characteristic keratoses or pigment irregularities on the trunk. Several authors have cited a similar association in exposed workers as evidence that arsenic may cause internal cancers, expecially of the lung (Braun, 1958; Currie, 1947; Hueper, 1951; Osburn, 1957; Robson and Jelliffe, 1963; Rosset, 1958; Roth, 1957b). In addition, the skin lesions are characteristically multiple and predominantly on the areas of the body that are protected by clothing. Both these features are notable, inasmuch as "ordinary" skin cancers tend to be single and have been shown to have a body distribution directly correlated with the amount of sun exposure (Birmingham, 1971; Miescher, 1934). Arsenical lesions (both keratoses and cancers) also appear at an earlier average age than do solar (senile) keratoses and related carcinomas (The National Research Council, 1977a).

The histopathology of the multiple and varied lesions seen in arsenism has been the subject of considerable interest among dermatopathologists (Anderson, 1932; Ayres and Anderson, 1934; Miescher, 1934; Montgomery, 1935; Pinkus and Mehregan, 1969; Yeh, 1963; Yeh, et al. 1968). Lesions that clinically are keratoses may show proliferation of keratin of a verrucous nature, may exhibit precancerous derangement of the squamous portions of the epithelium equivalent to those seen in Bowen's disease and solar keratosis, or may even be frank squamous cell carcinomas. Lesions that are less keratotic and more erythematous may contain either squamous cell or basal cell carcinoma or a mixture of cell types. Most authors seem to agree that keratotic lesions appear to be able to progress to frank carcinoma, but observation of such an event is rare, and most cancers appear to arise independently of the keratoses.

The question of the association of Bowen's disease with arsenism has stimulated considerable controversy. Graham and Helwig (1959) analyzed 36 autopsies of patients with Bowen's disease in whom arsenic intake had been ruled out as much as possible. It is striking that this group of patients differed from patients with arsenism in several respects: they lacked the typical keratoses and pigmentation; they had a tendency for the "typical Bowenoid" squamous cell carcinoma in situ to precede the other cutaneous malignancies by an average of 6 years; there was an incidence of approximately 80% of associated internal malignancies (some diagnosed only at autopsy); and they had suggestive evidence of a familial predisposition to the condition. Of more than 100 living patients with the diagnosis of Bowen's disease surveyed by the same authors, internal malignancy had been diagnosed in 23. These features seem sufficient to distinguish Bowen's disease from chronic arsenism, despite the confusion later introduced by Graham, et al. (1961). If Graham and Helwig's cases are representative, the association of systemic cancers is much higher in Bowen's disease than has ever been suggested for chronic arsenism (The National Research Council, 1977a).

The effects of arsenic exposure may occur many years after cessation of exposure (The National Research Council, 1977a).

Braum (1958) reported on 16 patients who had been exposed to arsenic in their occupation as vintners many years before. No known exposure to arsenic had occurred since. All had keratoses, nine had leukomelanoderma of the trunk, and seven had skin cancer or intraepidermal carcinoma *in situ*. Eight had lung cancer.

Roth (1957b) also studied 27 vintners whose arsenic exposure had occurred 10-14 years earlier. His population was selected by having come to autopsy. He found that 16 of the 27 had a total of 28 cancers, including five with skin cancer. There was hyperkeratosis of the palms and soles," particularly in the patients with tumors." Melanosis was also present, but hard to evaluate in the postmortem state.

For a few months in 1955, a large number of babies in Japan received a formula made from powdered milk contaminated with arsenic (Masahiko, O. and Hideyasu, 1973; Okamura, et al. 1956a,b; Satake, 1955). The subacute symptoms of poisoning in these infants included the usual coughing, rhinorrhea, conjunctivitis, vomiting, diarrhea, and melanosis, but the striking presenting features were fever and abdominal swelling secondary to hepatomegaly. Abnormal laboratory findings included anemia, granulocytopenia, abnormal electrocardiograms, and increased density at epiphyseal ends of long bones similar to the familiar "lead line." Nagai et al. (1956) reported on a group of these children who were followed for more than 6 months. Except for a measurable retardation in ulnar growth, they found that all other features of the syndrome had disappeared, including melanosis. Followup is continuing, and a report by the Japanese Pediatric Society (1973) indicated that growth was still reduced and that there was a probable incidence of leukomelanoderma in the children (aged 17-20 at the time) of 15-30%. The children had a 15% incidence of keratosis (Yamashita, 1972). Of greater concern, however, was the observation of increased incidences of mental retardation, epilepsy, and other findings that suggested brain damage in the arsenic-exposed children. Presumably, future studies in this population (more than 10,000 exposed infants) will help to resolve some of the standing questions regarding the latent effects of arsenic exposure.

Synergistic or Antagonistic Compounds. Moxon (1938) first demonstrated the protective effect of arsenic against selenium poisoning when he found that arsenic at 5,000 µg/l as sodium arsenite in the drinking water largely prevented liver damage in rats whose diet contained selenium at 15 µg/g as seleniferous wheat. Moxon and Dubois (1939) then showed that arsenic was unique in its ability to prevent selenium toxicity; all other elements tested were unable to protect against all manifestations of chronic selenosis. Sodium arsenite and sodium arsenate were equally effective against seleniferous grain, but the arsenic sulfides were ineffective (Dubois, et al. 1940). Arsanilic acid and 3-nitro-4-hydroxyphenylarsonic acid, two organic arsenicals used as "growth-promoters" for livestock, also exhibited a beneficial action against selenium poisoning in rats when given in the drinking water (Hendrick, et al. 1953). There is evidence that it would be practical to use these two agents to protect swine and poultry in high-selenium regions (Carlson, et al. 1954; Wahlstrom, et al. 1955). Amor and Pringle (1945) even suggested the use of an arsenic-containing tonic as a prophylactic agent against selenium poisoning in exposed industrial workers.

The metabolic basis for the beneficial effect of arsenic in selenium poisoning remained confused for some time, because arsenic was known to block the biosynthesis of dimethylselenide, a detoxification product in animals that received subacute doses of selenium by injection (Olson, et al. 1963). Moreover, the protective effect of arsenic against dietary selenium was not seen if the arsenic was given in the diet, instead of the drinking water (Ganther and Baumann, 1962); Frost (1967) has shown that the toxicities of arsenic and selenium are additive if both elements are given in the drinking water. These results agree with those of Obermeyer, et al. (1971) who recently observed an additive toxicity between arsenite and trimethylselenonium chloride or dimethylselenide.

Ganther and Baumann (1962a) studied the influence of arsenic on the metabolism of selenium when both elements are injected in subacute doses and found that the excretion of selenium into the gastrointestinal tract was markedly stimulated by arsenic. Levander and Baumann (1966a) observed an inverse relationship in arsenic-treated rats between the amount of selenium retained in the liver and the amount excreted into the gut; and they concluded that the bile might be the route by which selenium was appearing in the gastrointestinal tract. This hypothesis proved correct when it was discovered that in 3 hours over 40% of the selenium injected could be recovered in the bile of rats that also received arsenic, whereas only 4% of the selenium was excreted into the bile of rats not given arsenic (Levander and Baumann, 1966b). This effect of arsenic on the biliary excretion of selenium was not confined to subacute-toxicity experiments: a response of selenium to arsenic was seen at dosages approaching a rat's daily intake of selenium when fed some crude commercial diets. Sodium arsenite was the most effective form of arsenic in enhancing the biliary excretion of selenium, but arsenate and 3-nitro-4-hydroxyphenylarsonate were also active to some extent. In experiments with radioactive arsenic, it was found that selenium stimulated the biliary excretion of arsenic, just as arsenic stimulated the excretion of selenium. Initial attempts to characterize the forms of selenium in rat bile suggested that the element is probably present in several forms, including some macromolecularly bound selenium.

Although these studies provide physiologic information concerning the interaction of arsenic and selenium, the chemical mechanism of the process is still far from clear. The most logical hypothesis to account for the arsenic-selenium antagonism from the molecular point of view assumes that arsenic combines with selenium-perhaps, in analogy with sulfur chemistry, by reacting with selenol (-SEH) groups-to form a detoxification conjugate that passes readily into the bile (The National Research Council, 1977a).

Teratogenesis. Although no animal experiments have demonstrated the carcinogenicity of arsenic, several have shown that sodium arsenate induces developmental malformations in a variety of test animals: embryo chick, hamster, rat, and mouse (Ancel, 1946; Ridgeway and Karnovsky, 1952; Ferm and Carpenter, 1968; Hood and Bishop, 1972; Beaudoin, 1974).

Pregnant golden hamsters injected with sodium arsenate (15 to 25 mg/kg body weight) produced offspring with a range of developmental malformations including anencephaly, renal agenesis, rib malformation, cleft lip and palate, and anophthalmia. The percentages of living embryos with various selected malformations followed maternal treatment with 20 mg/kg sodium arsenate on the 8th day of gestation were as follows: nearly 90 percent with all malformations; over 80 percent with anencephaly; nearly 70 percent with rib malformations; 30 percent with exencephaly. The spectrum of malformations varied with the time of injection during critical stages of embryogenesis. Malformations induced by arsenate differed from those induced by other teratogenic agents including certain heavy metals (Ferm, et al. 1971).

In another study, single intraperitoneal injections of sodium arsenate (45 mg/kg) in Swiss-Webster mice between the 6th and 11 days of gestation consistently caused an increase in fetal resorptions, a significant decrease ($p<0.05$) in fetal weights compared to controls, and a number of fetal malformations, most frequently the following: exencephaly, shortening of the jaws with consequent protrusion of the tongue, exophthalmos, missing pinna, cleft lip, hydrocephalus, umbilical hernia, eventration, ectrodactyly, micromelia, and shortened or twisted tail or limb, or both. Malformations were dependent on the stage of embryogenesis. Exencephaly occurred in 54 percent of the fetuses when the injection was administered on day 9 of gestation; fusion of the ribs occurred in 100 percent of the fetuses when the injection was given on day 9; and fusion of the vertebrae occurred in 73 percent when the injection was given on day 10 (Hood and Bishop, 1972).

In a later report, Ferm (1977) demonstrated that administration of 20 mg/kg of sodium arsenate intravenously or intraperitoneally to Golden hamsters during day 8 to 9 of gestation induced a specific spectrum of malformations including exencephaly, encephaloceles, skeletal defects, and malformations of the genitourinary system. The last effect, which appears to be unique to arsenate, occurred in both sexes and with high frequency.

Ferm (1977) further showed that radioactive arsenic (^{74}As) injected intravenously into Golden hamsters on day 8 of gestation was transmitted across the placenta during the critical stage of embryogenesis and appeared in the fetal tissues. Ferm refers to a report by Lugo, et al. (1969) concerning a case of arsenic trioxide poisoning during human pregnancy, which demonstrated the "ease with which inorganic arsenic crosses the human placenta at term with extremely high levels in the fetal liver, brain, and kidneys" (Ferm, 1977). Introduction of arsenic into fertilized bird eggs has led to malformations of beak and brain (Peterkova and Puzanova, 1975).

Hood, et al. (1977) compared the prenatal effects of oral and intraperitoneal administration of sodium arsenate in mice. Intraperitoneal administration had a considerably greater effect than oral administration on prenatal mortality, reduction of fetal weights, and occurrence of fetal malformations. The dosages were 40 mg/kg (intraperitoneal) and 120 mg/kg (oral).

Hood, et al. (1977) further noted that although arsenite is considerably more toxic than arsenate, it has received less attention from teratologists. Intraperitoneal injection of mice in utero with 10 to 12 mg/kg of arsenite on one of days 7 to 12 of pregnancy caused significant increases in prenatal morality ($p<0.05$), and treatment on days 8, 9, and 10 resulted in gross and skeletal malformations similar to but less frequent than those induced by comparably toxic levels of arsenate (Hood et al. 1977).

Mutagenesis. Most mutagenesis research has centered on chromosomal reactions to sodium arsenate. There are no data based on the host-mediated assay or the dominant lethal technique (The National Research Council, 1977a).

One of the earliest observations that has meaning today was made by Levan (1945). Root meristem cultures of Allium cepa were treated for 4 hours with an unspecified arsenic salt at 10 concentrations, from lethal to a no-effect. Chromosomal changes were observed, including spindle disturbances and metaphase arrests. Similar effects, with minor variations, were observed after treatment with salts of 24 other metals (mostly nitrates). The changes resembled those caused by colchicine, but they cannot be considered serious damage (The National Research Council, 1977a).

Petres and Hundeiker (1968) and Petres, et al. (1970 and 1972) have reported chromosomal breakage in human leukocyte cultures after short-term in vitro exposure to sodium arsenate and in cultures obtained after long-term exposure to arsenical compounds in vivo.

The cytotoxic and mutagenic effects of sodium arsenate were tested *in vitro* on phytohemagglutinin-stimulated lymphocyte cultures in concentrations of 0.05-30 µg/ml of culture medium (Petres, et al. 1970). It was reported that 33% of metaphase plates were pulverized at 0.1 µg/ml and 80-100% at concentrations of 2 µg/ml or greater. The "mitosis index" and the "(3H)thymidine labeling index" were decreased. Arsenate has also been found to increase the total frequency of exchange chromosomes in *Drosophila melanogaster* treated with selenocystine, (Walker and Bradley, 1969), and several organic arsenicals have a harmful synergistic effect on the number of abnormalities in barley chromosomes caused by ethylmethane sulfonate (Moutschen and Degraeve, 1965). The overall significance of these chromosomal studies is difficult to assess, inasmuch as many unrelated compounds may cause similar effects. The fact that arsenic compounds have caused chromosomal damage in a number of biologic systems, however, should alert toxicologists to a possible role of arsenic in chemically induced mutagenesis (The National Research Council, 1977a).

The *in vivo* studies were made on 34 patients at the University of Freiburg skin clinic (Petres, et al. 1970). Thirteen of these patients had had intensive arsenic therapy, some more than 20 years before the experiment; most of these were psoriasis patients. The control group (21 patients) consisted of 14 psoriasis patients and 7 with eczema, none of whom had had arsenic treatment. Phytohemagglutinin-stimulated lymphocyte cultures were prepared from each patient for evaluation of chromosomal aberrations. The incidence of aberrations was remarkably greater in the cultures of patients who had been treated with arsenic. Expressed as the frequency per 1,000 mitoses, secondary constrictions were 49 in the arsenic group and 12 in the control, gaps were found in 51 in the arsenic group and 7 in the control, "other" lesions were 26 in the arsenic group and 1 in the control, and broken chromosomes were 65 per 1,000 mitoses in the arsenic group and 2 in the control. Aneuploidy was found at the expected frequency in the arsenic group. The extent of abnormalities attributed to treatment with arsenicals is impressive; it is important that this study be repeated (The National Research Council, 1977a).

Paton and Allison (1972) investigated the effect of sodium arsenate, sodium arsenite, and acetylarsan on chromosomes in cultures of human leukocytes and diploid fibroblasts. Subtoxic doses of the arsenicals were added to leukocyte and fibroblast cultures at various times between 2 and 48 hours before fixation. In leukocyte cultures treated with sodium arsenite at 0.29-1.8 x 10^{-8}M for the last 48 hours of the culture period, 60% of 148 metaphases examined were found to have chromatid breaks. No significant breaks were found in cultures treated with sodium arsenate at 0.58 x 10^{-8}M, the highest nontoxic concentration. However, treatment with acetylarsan at 6.0 x 10^{-8}M resulted in 20% chromatid breaks in 50 metaphases examined. Sodium arsenite caused chromosomal damage in diploid fibroblasts to which sodium arsenite (0.29-5.8 x 10^{-8}M) was added to the medium for the last 24 hours of culture; chromatid breaks were found in 20% of 459 metaphases examined. These results supported the in vitro observations of Petres et al. (1972) and Petres and Hundeiker (1968).

Carcinogenicity. The National Research Council (1977) has thoroughly reviewed the literature concerning the carcinogenicity of arsenic. Most of the material in this section is taken from that review.

The clinical association of skin cancer with the oral administration of arsenic compounds began with a report by Hutchinson (1888). He described six patients in whom skin cancer occurred and who had suffered for very long periods from diseases of the skin (five with psoriasis, one with pemphigus).

multiple lesions. Multiple lesions occurred even when squamous cancers arose in keratoses; there was an average of two lesions per case.

The elapsed time from the beginning of administration of the arsenical drug to the beginning of the epitheliomatous growth was variable, but averaged 18 years, regardless of the type of lesion. In cases with keratosis, the latent period to the onset of keratosis was about half the latent period to the onset of the epithelioma-i.e., about 9 years. In spite of the long induction period, arsenic-related skin cancers started when the patients were relatively young, one-third when they were 40 or younger, and 70% when they were 50 or younger.

Of the 143 patients, 13 had or developed miscellaneous cancers at other sites, but such cases were not reported systematically; the reports commonly presented one or a few case histories. For example, Regelson, et al. (1968) reported a case of hemangioendothelial sarcoma of the liver in a 49-year-old man who had taken Fowler's solution intermittently for 17 years to control psoriasis.

There have been numerous reports of arsenic-induced occupational cancer, such as those of the excess lung-cancer mortality among Southern Rhodesian miners of gold-bearing ores containing large amounts of arsenic (Osburn, 1957) and of the occurrence of lung and liver cancer and clinical arsenism among German vineyard workers exposed to arsenic-containing insecticides (Braun, 1958; Roth, 1957a,b). The association of cancer with a high degree of arsenic exposure has often been based on the existence of palmar or plantar keratoses (Sommers and McManus, 1953). However, because of the increased concentration of arsenic in the lesions of Bowen's disease, arsenic has been considered as a possible cause of the disease and accompanying visceral tumors

(Graham, et al. 1961), without overt prior exposure to arsenicals.

A number of relatively quantitative studies of cancer attributable to occupational exposure to arsenicals will be discussed in some detail.

A death-record examination was made of a British plant that manufactured sodium arsenite sheep dip (Hill and Faning, 1948; Perry et al. 1948). The factory was in a small country town within a specific birth and death registration subdistrict. In this and adjacent subdistricts, death certificates of 75 factory workers and 1,216 men (not factory workers) in three other occupational groups were obtained for the period 1910-1943. Of the 75 deaths among factory workers, 22 (29%) were due to cancer; of the other 1,216 deaths, 157 (13%) were due to cancer. The proportion of deaths due to cancer was even higher among men who actually worked with the manufacture and packaging of the arsenic-containing material: 16 of the 31 deaths of men so classified were due to cancer. The number of deaths due to cancer according to site for the two groups is shown in Table 6, in which those deaths are expressed as a fraction of cancer deaths and as a fraction of total deaths. The absolute numbers of deaths and the fraction of cancer deaths are from the author's paper; the fractions of total deaths were calculated for this report. The data suggest a relative excess in the factory workers of cancers of the respiratory system and skin, whether calculated on the basis of cancer deaths or of total deaths; the corresponding deficits in cancers of the digestive organs and peritoneum disappear when calculated on the basis of total deaths.

Although Hill and Faning (1948) stated that the numbers of cancer deaths are small, they concluded that "there is a suggestion in the figures that the factory workers have been especially affected in the lung and skin." Hence, there was an investigation of the environmental conditions at the factory and the clinical condition of the workers in question, compared with employees in other branches of the factory who were not exposed to arsenic (Perry, et al. 1948). The median air arsenic content for the chemical workers at the various operations ranged from 254 to 696 μg/m^3. As an upper limit, this was stated to represent the inhalation of about 1 g of arsenic per year. This amount of arsenic is roughly equivalent to the amount received by patients getting arsenic medication for skin diseases (The National Research Council, 1977a).

The excretion of arsenic in the urine of 127 current employees was determined; the scatter of these values was very wide. Some exposed workers excreted from 1 to nearly 2 mg/day, whereas many excreted less than 100 μg/day. A few of the persons in the control group had very high excretion rates, for which the authors found no explanation. It is important to note that 20 of the 31 factory workers had been exposed to airborne sodium arsenite for more than 20 years, and five of them for 40-50 years. Furthermore, the median age of the 31 exposed workers was 52 years, and the average age was 50. None of these men's lungs had pathologic signs attributable to their exposure to sodium arsenite (radiographs were made, and vital capacity and exercise capacity were measured).

The mortality experience of 8,047 white male smelter workers exposed to arsenic trioxide during 1938-1963 was compared by Lee and Fraumeni (1969) with that of the white male population in the same state. There was a threefold excess total mortality from respiratory cancer in smelter workers, and this reached an eightfold excess for employees working more than 15 years and heavily exposed to arsenic. When respiratory cancer deaths were grouped according to degree of arsenic exposure, the observed mortality was significantly higher than expected in all three groups: approximately 6.7, 4.8, and 2.4 times the expected mortality in the heavy-, medium-, and light-exposure groups, respectively. In addition to arsenic trioxide dust, smelter workers were concurrently exposed to sulfur dioxide. Exposure to silica and ferromanganese and lead dusts occurred in parts of the refineries where arsenic concentrations were low. Therefore, a similar classification was made for relative sulfur dioxide exposure. Respiratory-cancer mortality was directly related to sulfur dioxide exposure, with observed deaths ranging from 6.0 down to 2.6 times the expected in heavy-, medium-, and light-exposure groups. Most work areas having heavy arsenic exposure were also medium-sulfur dioxide areas, and all jobs with heavy sulfur dioxide exposure were medium-arsenic areas. It was observed that workers with the heaviest exposure to arsenic and moderate or heaviest exposure to sulfur dioxide were most likely to die of respiratory cancer.

A study by Pinto and Bennett (1963) involved a smelting plant in the state of Washington that produced arsenic trioxide as a by-product. The plant had an average employment of 904 during the years 1946-1960. During that period, a total of 229 deaths were reported among active plant employees and pensioners. Thirty-eight of the dead were classified as exposed to arsenic. Of the 38, six died of cancer, including three cases of cancer of the respiratory tract. The total cancer experience of the arsenic-exposed workers was not higher than that of the unexposed, although there was twice as much respiratory cancer in both exposed and unexposed smelter workers as expected from male mortality experience in Washington. Mortality among workers at the same plant was restudied by Milham and Strong (1974). They criticized the methods of the Pinto and Bennett study. The records of workers from the same plant revealed 40 deaths from lung cancer, which was signicantly higher than the 18 expected on the basis of rates in the general U.S. population.

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Snegireff and Lombard (1951) made a statistical study of cancer mortality in a metallurgic plant (A) in which arsenic was handled and in a control plant (Z) in which "working conditions approximate those of Plant A except that no arsenic is handled." From 1922 to 1949, there were 146 deaths among the employees of Plant A who handled large quantities of arsenic trioxide. Of these deaths, 18 were due to cancer, including seven cases of cancer of the respiratory system. In the control plant, 12 of 109 deaths between 1941 and 1949 were due to cancer, including six due to lung cancer. The authors stated that total cancer mortality in the two plants was not significantly different from the figures for the state as a whole, and they concluded that handling of arsenic trioxide in the industry studied does not produce a significant change in cancer mortality of the plant employees. However, as pointed out in the National Institute for Occupational Safety and Health (NIOSH) publication, Occupational Exposure to Inorganic Arsenic New Criteria-1975, (U.S. Department of Health, Education and Welfare, 1975), there are a number of deficiencies in the report. Specifically, reanalyses of the data have revealed that actually there was a large excess (approximately five-fold) of lung-cancer deaths relative to mortality from all causes among workers in both plants. Thus, the data demonstrated evidence of a carcinogen for the respiratory system among the workers of both the plant in which arsenic trioxide was handled and the control plant.

Findings of increased risk of lung cancer among copper-smelter workers are not limited to the United States. A retrospective study by Kuratsune,et al. (1974) in Japan revealed that, of 19 males who died of lung cancer in a particular town, 11 had been employed as smelter workers in a local copper refinery, and in all cases the disease had become manifest after the men had stopped working at the refinery. The author's conclusion was that prolonged exposure to arsenic, and possibly also other compounds, seemed to be associated with cancer of the lungs. Additional groups exposed to inorganic arsenic-such as gold miners in Rhodesia (Osburn, 1969) hard-rock miners in the United States (Wagoner, et al. 1963), and nickel refinery workers (Rockstroh, 1959) - have shown an increased mortality from lung cancer, but evaluation of the role of arsenic is difficult, because of the presence of other carcinogens in the working atmosphere.

A study at the Dow Chemical Company examined the incidence of respiratory cancer among 173 decedents who were exposed primarily to lead arsenate and calcium arsenate and 1,809 decedents who worked in the same plant and were not exposed to those compounds (Ott, et al. 1974). Data were presented on the relationship between cumulative arsenic exposure and the ratio of observed to expected deaths from lung cancer. The average exposure of each worker was calculated on the basis of records of job assignments and data on the arsenic content of the air in various parts of the plant. Deaths from respiratory malignancy were 7 times greater than expected for total inhaled quantities of 29.8 g and 2-4 times greater for 0.13-6.56 g. There was no association between the extent of exposure and the time from beginning of exposure to death; most of the respiratory cancers occurred 20-40 years after initial exposure, regardless of total exposure.

The ratio of observed to expected deaths was even higher (3.85 : 1) in another category-malignant neoplasms of the lymphatic and hematopoietic tissues except leukemia-than it was in malignant neoplasms of the respiratory system (3.45 : 1). Six lymphomas were reported, with the following diagnoses on the death certificates: four cases of Hodgkin's disease, one of lymphoblastoma, and one of reticulum cell sarcoma.

By contrast with the Dow Chemical Company workers, orchard workers who sprayed lead arsenate showed no evidence of increased cancer (Nelson, et al. 1973). A mortality study involving a cohort of 1,231 workers in Wenatchee, Washington, who had participated in a 1938 morbidity survey of the effects of exposure to lead arsenate insecticide spray was conducted in 1968-1969. Air concentrations of arsenic during spraying averaged 0.14 mg/m^3. The population was grouped according to exposure in three categories and compared in terms of standardized mortality ratios with the mortality experience of the state of Washington. There was no evidence of increased mortality from cancer, heart disease, or vascular lesions.

In 1974, the mortality experience of retired employees of an Allied Chemical Company pesticide plant in Baltimore was analyzed (Baetjer, et al. 1975; National Research Council, 1977). The employees had been exposed to a number of industrial chemicals, including arsenicals; there were no data on the extent of exposure to the various chemicals. Incidence of death among the retirees was 3.5 times that among the general Baltimore population. The excess mortality was concentrated in cancer-caused deaths (14 times the expected), particularly respiratory cancer and lymphatic cancer. The non-cancer deaths were at the expected rates. These calculations were based on a total of 22 deaths in men from all causes during the period 1960-1972.

Several human studies not generally available were reviewed in the National Institute of Occupational Safety and Health document on occupational exposure to inorganic arsenic (U.S. Department of Heath, Education, and Welfare, 1975), including unpublished reports to Kenncott Copper Corporation in 1971 and 1974; unpublished papers presented at the conference on occupational carcinogenesis in New York City on March 24-27, 1975; and an evaluation by the National Institute of Occupational Safety and Health (NIOSH) of the study by Nelson, et al. (1973). In the last examples, independent sources of information investigated by NIOSH contradicted, rather than confirmed, the report by Nelson, et al. (1973). The conclusion drawn was that the report apparently did not accurately depict the cancer incidence of persons exposed to lead arsenate spray in the Wenatchee Valley (U.S. Department of Health, Education and Welfare, 1975).

High incidences of skin cancer have been reported in several population groups exposed to high concentrations of arsenic in drinking water, including people in the district of Reichenstein in Silesia, (Geyer, 1898), Cordoba Province in Argentina, (Bergoglio, 1964), and Taiwan (Tseng, et al. 1968).

Chronic arsenical poisoning, including skin cancer and a gangrenous condition of the hands and feet called Blackfoot's disease, has occurred in several communities exposed to arsenic in drinking water. The best-documented instance of such arsenical poisoning is in Taiwan (Yeh, et al. 1968; Yeh, 1963, 1973; Tseng, et al. 1968; Tseng, 1977). In a house-to-house survey of 40,421 people in 37 villages along the southwest coast of Taiwan, Tseng, et al. (1968) found that the prevalence of skin cancer, hyperpigmentation, and keratosis each correlated with the arsenic content of the water. The highest range of concentrations was greater than 0.6 ppm, and the lowest range was less than 0.29 ppm. From a general survey of these inhabitants, the prevalence rate for arsenical skin cancer was 10.6 per 1,000 residents in 1965. The skin cancer rate for well water containing >0.60 ppm was 21.4 per 1,000 people, while at <0.29 ppm it was 2.6.

The sources of drinking water for these areas were deep artesian wells, used from 1910/20 until 1966, when a tap water supply was installed. The concentrations of arsenic in the water ranged from 0.01 to 1.82 ppm (median range was 0.4 ± 0.6 ppm). The chemical form of arsenic in the water was not determined, but it may have been either trivalent (because the well water is probably anaerobic) or a methylated arsine (because the authors observed a combustible gas [perhaps methane] bubbling from the water storage tanks). Attempts to measure the arsenate to arsenite ratio of the water have been confined to measurements in a United States laboratory of a sample shipped from Taiwan with no special precautions to preserve the speciation occurring at the collection point (Irgolic, 1978). The arsenate to arsenite ratio in two samples was 10 to 1 and 7 to 1, with a total arsenic concentration of approximately 0.6 ppm. Since the native water is likely to be anaerobic and since oxidation probably took place to some degree in transit to the analysis laboratory, the ratio in the natural water is probably less than 10 but cannot be assessed at this time. Therefore, from the best available information, people in that region of Taiwan could have been exposed to both trivalent and pentavalent arsenic compounds.

Assessing the Taiwan situation is more complex than simply identifying the two oxidation states of arsenic, as reported recently by Lu, et al. (1975, 1977a,b). These workers have observed non-arsenical fluorescent compounds in water samples from the areas where Blackfoot disease is endemic and have identified one of the fluorescent components as an alkaline hydrolysate of ergotamine, lysergic acid, or a related compound (Lu, et al. 1977b). They have also shown that one of the fluorescent components produced abnormalities in developing chick embryos (Lu, et al. 1977a). It is not known whether ergotamine was the compound that produced these abnormalities.

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The existance of arsenical waters in an eastern area of the province of Cordoba, Argentina, has been known for many decades and is associated with the occurrence of hyperpigmentation, keratosis, and skin cancer. A study made in 1949-1959 indicated a higher proportion of deaths from cancer in the arsenical region than in the rest of the province—23.8% versus 15.3% (Bergoglio, 1964). The excess was due mainly to cancer of the respiratory and digestive tracts in both men and women. The excess cancer was unrelated to socioeconomic differences.

In general, animal studies have not shown carcinogenicity for arsenic compounds, even when administered at near the maximally tolerated dosage for long periods. Two notable exceptions are described first, and then several of the negative studies (The National Research Council, 1977).

In 1962, Halver reported the occurrence of hepatomas in trout fed a synthetic diet containing carbarsone at 4.8 mg/g of diet (the data were reviewed by Kraybill and Shimkin (1964); the original report is not readily available). Of 50 trout exposed to carbarsone, five developed hepatomas. There were no hepatomas in a large control group fed the synthetic diet without carbarsone. However, aflatoxin contamination of the diet may have been a confounding variable.

More recently, Osswald and Goerttler (1971) reported that subcutaneous injections of sodium arsenate in pregnant Swiss mice caused a considerable increase in the incidence of leukemia in both the mothers and their offspring. A 0.005% aqueous sodium arsenate solution was injected daily during pregnancy for a total of 20 injections, each containing arsenic at 0.5 mg/kg. Some groups of offspring from the arsenic-treated females were given an additional 20 subcutaneous injections of arsenic (0.5 mg/kg) at weekly intervals. Leukemia occurred in 11 of 24 mothers (46%), 7 of 34 male offspring (21%), 6 of 37 female offspring (16%), and, in the offspring given the additional 20 injections, 17 of 41 males (41%) and 24 of 50 females (48%). Leukemia developed in only 3 of 35 male (9%) and in none of 20 female offspring of untreated control mice. Furthermore, 11 of 19 mice (58%) developed lymphoma after 20 weekly intravenous injections of 0.5 mg each of arsenic as sodium arsenate.

Long-term studies of effects of arsanilic acid on chickens, pigs, and rats were reported by Frost, et al. (1962). No adverse effects were seen in the chickens and pigs after 4 years of feeding, nor in pigs fed 0.01% arsanilic acid for three generations. Male and female weanling rats from the F_2 generation of a six-generation breeding study in which 0.01% and 0.05% arsanilic acid was fed were held on the 0.01% arsanilic acid diet or on the control diet for 116 weeks. The overall tumor incidence was the same in all groups and resembled the historical incidence of tumors in the colony, 35%-45%. The significance of these data lies in the fact that transplacental exposure to a carcinogen followed by lifetime exposure to the same carcinogen is often the most sensitive technique for detecting carcinogenicity of a substance (Tomatis and Mohr, 1973), but this test was negative.

Boutwell (1963) used female mice (Rockland and a specially bred strain highly susceptible to skin tumors) in a test for cocarcinogenicity of potassium arsenite. It was tested as an initiator, both orally by stomach tube (a total of 2.4 mg in 5 days) and locally (a total of 1.2 mg in eight applications during 5 days). This initiating treatment was followed by topical application of croton oil twice a week for 18 weeks. He also tested potassium arsenite as a promoter by daily applications (a total of 2.3 mg/week) after a single 75-µg dose of dimethylbenzanthracene (DMBA). The prolonged skin applications of potassium arsenite were hyperkeratotic and ulcerogenic. Other experiments were done to determine whether arsenic would increase the yield of skin cancers caused by a suboptimal regimen of DMBA plus croton oil given either at the time DMBA initiation or during the 24-week period of croton oil promotion. Under the latter condition, the mice were fed potassium arsenite at 169 µg/g of food. This dietary concentration of 169 µg/g (as potassium arsenite) is very high, compared with the 0.5 µg/g usually found in the human diet. In no case was there an effect of arsenite on skin carcinogenesis in these experiments. Many tumors developed in the positive control mice, beginning as early as 6 weeks after treatment began.

Baroni, et al. (1963) carried out a similar study with male and female Swiss mice, testing the oral effects of potassium arsenite (100 mg/l in drinking water) as an initiator with croton oil promotion and as a promoter with DMBA and urethane initiation. Local skin applications of sodium arsenate were tested as a promoter after initiation with DMBA or urethane. The arsenicals had no effect on tumorigenesis; and only a very slight degree of keratosis was observed.

Milner (1969) used three stains of mice that differed in susceptibility to the induction of skin tumors by the application to the skin of methylcholanthrene-impregnated paraffin disks for 2-3 weeks. The treated site was transplanted syngeneically and observed for 8 weeks for tumor formation.

Arsenic trioxide (100 mg/l in drinking water) was administered either during methylcholanthrene exposure, to animals with transplanted skin, or both. Arsenic exposure produced a small increase in the yield of papillomas in the low-susceptibility strain, a small decrease in the high-susceptiblity strain, and no effect in the intermediate-susceptibility strain.

Byron, et al. (1967) fed either sodium arsenite or sodium arsenate to Osborne-Mendel rats in a 2-year study at dietary concentrations of 15-250 µg/g for arsenite and 30-400 µg/g for arsenate. No carcinogenic activity of either material was found. These investigators also did a 2-year arsenic feeding experiment on dogs, with negative results; however, this was an inadequate observation period for studying carcinogenic responses in dogs.

Hauper and Payne (1962) incorporated arsenic trioxide in the drinking water (either plain or with 12% ethanol) of groups of rats and mice. The initial concentration of 4 mg/liter was increased by 2 mg/liter each month to a maximum of 34 mg/liter at 15 months. Thus, the daily intake of arsenic trioxide ranged from 0.1 to 0.8 mg/rat. The administration of arsenic trioxide was continued until 24 months. Neither the rats nor the mice developed any cancers in suspected target organs-skin, lung, and liver.

Kanisawa and Schroeder (1969) and Schroeder, et al. (1968) found no carcinogenic effects on mice exposed from weaning to senescence to potassium arsenite at 5 mg/l in drinking water (Kanisawa and Schroeder, 1969) or on rats on the same regimen (Schroeder, et al. 1968).

Kroes, et al. (1974) studied the carcinogenicity of lead arsenate and sodium arsenate with SPF-Wistar-derived male and female rats. In addition, some groups were intubated with a subcarcinogenic dose of diethylnitrosamine to investigate a possible synergistic action leading to lung tumors. Food intake and body weights were recorded, and complete gross and microscopic examinations were made on all animals. Lead arsenate that was incorporated in the diet at 1,850 µg/g was toxic and caused increased mortality; an adenoma of the renal cortex and a bile duct carcinoma were found in this group, but no significance can be attached to one or two tumors in any group. No cancer was associated with the feeding of lead arsenate at 463 µg/l or sodium arsenate at 416 µg/l. No synergism with the nitrosamines was observed. There was a high spontaneous-tumor incidence in this experiment. The test diets were fed to female rats from the time of parturition until the young were weaned, and these young were the test animals. Surviving rats were killed after 29 months of feeding.

As Fraumeni (1975) has pointed out, it is largely because laboratory studies have not succeeded in producing tumors in animals that arsenic has not been accepted universally as a carcinogen.

Evaluation of Carcinogenic Data. There is evidence from clinical observations and occupational and population studies that inorganic arsenic is a skin carcinogen in man. There is a characteristic sequence of skin effects of chronic exposure to arsenic that involves hyperpigmentation initially, then hyperkeratosis (keratosis), and finally skin cancer (Yeh, et al. 1968). This sequence has been observed under a variety of circumstances involving chronic exposure: potassium arsenite (Fowler's solution) was used medicinally (Neubauer, 1947), vineyard workers used sprays and/or dusting powders containing arsenic compounds and drank arsenic-contaminated wine (Braun, 1958; Roth, 1957b), chemical workers manufactured sodium arsenite for use as a sheep dip (Perry, et al. 1948), and residents of a southwest area of Taiwan had as their only source of drinking water for over 45 years artesian wells contaminated by arsenic from geologic deposits (Tseng, et al. 1968). The similarity of responses under these diverse circumstances is important, because studies in human populations always involve variables that cannot be controlled as in laboratory experiments; hence, the credibility of information derived from human studies depends on the demonstration of comparable effects under different conditions. This requirement has been amply met with arsenic as a cause of skin cancer (The National Research Council, 1977a).

The earliest skin effect of chronic arsenic exposure, hyperpigmentation (melanosis), occurs in a dappled pattern predominantly in unexposed areas. After the onset of melanosis, the skin begins to atrophy in a patchy way in hyperpigmented areas, with the formation of keratoses that are the pathognomonic lesions of chronic arsenic exposure (Yeh,et al. 1968). Only a small proportion of the keratoses evolve into skin cancer, and this takes place only after very many years. The sequence is illustrated by the Taiwan data-the prevalence of melanosis, keratosis, and skin cancer reached 10% in the male population roughly at ages of 18, 30, and 60 years, respectively (Tseng,et al. 1968). Chronic exposure to inorganic arsenic thus causes a slowly progressive form of patchy skin damage involving the epidermis and adnexal structures, as well as the underlying dermis, with the precancerous keratoses and cancers forming in the areas of chronic atrophy. The chronic damage and tumorigenesis resulting from arsenic are similar to the effects of ionizing and ultraviolet radiation on the skin (The National Research Council, 1977a).

Arsenical skin cancer is readily distinguished from skin cancer induced by sunlight, in the it occurs predominantly on surfaces that are shielded from sunlight and multiple lesions are much more common; for example, in 428 of the 429 cases of skin cancer studied in Taiwan, there was more the one cancer (Yeh,et al. 1968).

Substantial doses of inorganic arsenic are required to produce an appreciable incidence of skin cancer. The average intake of persons treated with Fowler's solution who developed skin cancer was around 20-30 g. The prevalence of skin cancer in Taiwanese men exposed to drinking water containing arsenic at 300-600 mg/l was about 15% at age 60 and over. The normal incidence is 2-3%. On the basis of a 2-liter/ day water intake for the period over which the artesian wells were used (45 years), the total arsenic intake must have been about 15 g, which is roughly in the same domain as that in clinical cases of the use of Fowler's solution. Thus, the Taiwanese data that demonstrated the requirement for large doses of arsenic to obtain even a modest yield of skin cancer are consistent with the relatively low frequency of skin cancer in patients treated with Fowler's solution. The low potency of inorganic arsenic may explain why no skin effects have been reported in people treated for syphilis with organic arsenicals, inasmuch as the total doses amounted to only a few grams. However, it is also possible that the metabolism of the organic arsenicals is sufficiently different to preclude the occurrence of skin cancer and other forms of arsenical damage even at higher doses (The National Research Council, 1977a).

The relative frequency of melanosis, keratosis, and skin cancer was roughly similar in the Taiwanese population and the chemical workers who manufactured sheep dip. On direct examination, the latter showed a 90% prevalence of melanosis and a 30% prevalence of keratosis, for a ratio of melanosis to keratosis of 3 : 1. At comparable ages, the Taiwanese showed a ratio of about 4 : 1. Two of the nine keratosis patients in the sheep dip factory had already been treated for skin cancer, and the proportionality between keratosis and skin cancer was about the same in Taiwan. As in the Taiwan experience, the sheep-dip chemical workers had been exposed to large doses of inorganic arsenic (up to 1 g/year), but much of this was by inhalation (The National Research Council, 1977a).

It is possible that the trivalent and pentavalent forms of inorganic arsenic produce the same effects on skin. This is of interest, particularly in view of the different metabolic patterns of trivalent and pentavalent inorganic arsenic - the former by interaction with sulfhydryl groups and the latter by substituting for phosphate. The clinical use of Fowler's solution and the manufacture of sodium arsenite as a sheep dip both involved exposure to trivalent inorganic arsenic. The two categories of people developed similar skin responses. The Rhodesian gold miners, in whom the incidence of typical arsenical keratoses was very high, were exposed to arsenopyrite, in which the arsenic becomes trivalent on weathering; the reactions of arsenopyrite in the body are unknown (The National Research Council, 1977a). The chemical form of arsenic in the Taiwanese artesian-well water is also unknown; however, the reported occurrence of methane gas in the water could preclude the existence of arsenic in the pentavalent form (The National Research Council, 1977a).

Of the published reports on mortality from respiratory cancer in copper smelters, the most impressive is that of Lee and Fraumeni (1969). The study involved a population of 8,047 white male smelter workers who were followed for 26 years; for each employee, information was available on time, place, and duration of employment, maximal arsenic and sulfur dioxide exposures (descriptive, rather than numerical), and cause of death. The life-table method was used to evaluate age-specific mortality rates for the various causes of death, and the rates were compared with those of the states in which the smelters were. The number of deaths available for analysis was very substantial-1,877.

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The study demonstrated a systematic gradient for respiratory cancer according to the magnitude and duration of exposure to both arsenic and sulfur dioxide. These agents, however, were inseparably linked, because of the nature of the smelter operations. The amount of excess cancer was impressive, with an eightfold increase in the workers who had the heaviest arsenic exposure for the longest duration, i.e., more than 15 years. The latent period-the interval between first employment and death from respiratory cancer-was extraordinarily long and was inversely related to the magnitude of exposure: 34, 39, and 41 years for the categories of heavy, medium, and light arsenic exposure. There were deficiencies in the study, some of which were unavoidable. For example, no indication was given of whether the study population was representative of the total worker population; the exposure rankings were based on the maximal arsenic concentrations, rather than weighted averages derived from work histories. No quantitative data were available on exposure. No attempt was made to validate the stated causes of death. No smoking histories were obtained. However, none of these deficiencies could be seriously regarded as invalidating the conclusions of the study (The National Research Council, 1977a).

The Kuratsune, et al. (1974) report dealt with a smaller study that compared lung-cancer mortality rates calculated from the 22 deaths that occurred in a 30-year period in a smelter town with the lung-cancer experience in the same period in a neighboring city and in Japan as a whole. The standardized mortality rate for males in the smelter towns was 4 times higher than that for the rest of the country, but equal to that for women. This fourfold excess is comparable with the 3.3-fold excess observed in the Lee-Fraumeni study. Although many of the men in the town worked in the refinery, a much higher proportion of the lung-cancer cases, compared with controls, occurred in men who were heavily exposed to arsenic as smelter operators. As in the case of the Lee-Fraumeni study, the latent period from first exposure to the diagnosis of lung cancer was very long, ranging from 26 to 48 years. The duration of employment was also very long, with a median of about 30 years, although two cases occurred in people who worked for only 2-3 years.

Two lung-cancer studies of the American Smelting and Refining Company smelter have produced conflicting results. The 1963 Pinto and Bennett report examined the proportional mortality from lung cancer in a total of 229 deaths in the period 1946-1960. This study dealt only with pensioners and workers who died during their employment and did not include people who had left the plant. The reported data showed that the 18 lung-cancer deaths in the plant population as a whole indicated that was higher than the rate in the state of Washington. However, the excess lung cancer for the plant as a whole was due to the high occurrence in controls, i.e., in workers who were considered not to have arsenic exposure. Milham and Strong (1974) by contrast, found, in the years 1950-1971, that there were records of 39 deaths due to respiratory cancer in Pierce County (the smelter locale) in people who were stated to have worked at the smelter. Application of U.S. mortality rates to the published figures for the smelter population at risk yielded an expected number of 18 respiratory-cancer deaths, compared with the 39 deaths observed (The National Research Council, 1977a).

Pinto, et al. (1963) recently resolved the discrepancy between the Pinto and Bennett (1963) and Milham and Strong (1974) papers in a study of the same smelter that reevaluated the exposure categories used in the Pinto and Bennett paper (1963) (which were apparently in error) and also included a longer observation period and therefore more deaths. The data, in Table 6, included a total of 32 respiratory-cancer cases and show a progressive increase in standardized mortality ratio with increasing arsenic exposure. The arsenic-exposure index was calculated as a weighted average based on urinary arsenic concentration and duration of employment. It is of interest that the eightfold excess in respiratory cancer for workers with the highest exposures and the threefold excess for all the smelter workers reported by Pinto et al. (1963) (see Table 6) were very close to the figures reported by Lee and Fraumeni (1969) and Kuratsune, et al. (1974) (The National Research Council, 1977a).

The studies described here indicated that excess respiratory cancer occurs in copper-smelter workers as a function of the magnitude and duration of exposure to arsenic, with latent periods of three to four decades from the time of initial exposure. However, the studies do not permit a resolution of the issue of whether concomitant exposure to sulfur dioxide and other smelter dusts is necessary for the carcinogenic response. Evidence from studies involving entirely different circumstances of exposure-including workers in three pesticide manufacturing plants (Hill and Faning, 1948; Ott, et al. 1974), vintners who applied pesticides (Braun, 1958), and Rhodesian gold miners (Osburn, 1969)-suggests that sulfur dioxide and other unspecified smelter dusts are not essential cofactors for the respiratory carcinogenicity of arsenic. All the nonsmelter studies had obvious limitations, but the lung-cancer excess in each study was relatively large and, taken as a group, they provide significant evidence that arsenic is a lung carcinogen (The National Research Council, 1977a).

The Hill-Faning (1948) study of 75 deaths in a sheep-dip factory used the indirect method of proportional mortality to evaluate the small group of 22 deaths from cancer; seven of them were cancers of the respiratory tract, compared with an expected 2.4 deaths. The Dow arsenic workers (Ott et al. 1974) were evaluated in two ways: by an analysis of death records of those who died from lung cancer (28, or 16.2%, of 173 chemical-worker deaths, compared with 104, or 5.7%, of the 1,809 control-case deaths), and then, as a retrospective cohort study, a comparison of the mortality from respiratory cancer (obtained from the records used in the first approach) among 603 persons identified as having worked in the arsenic plant from 1940 to 1973 with the mortality among the corresponding U.S. white population. The two approaches gave essentially the same results-a threefold to fourfold excess. However, the puzzling aspect of the data is that almost 60% of the respiratory-cancer deaths were in people who had worked with arsenic for less than a year, three decade earlier. Most of the arsenic workers were unskilled short-term employees, of whom a large proportion left the company after a brief period of employment. The followup study, however, dealt only with the people who remained in the company. A confirmation of the excess lung cancer in a followup of short-term arsenic workers who left the company would be very useful. Nevertheless, there were about a dozen cases in people who worked longer than a year and who were in the highest dose categories, where the excess risk was maximal-fourfold to sixfold. It is possible that the apparent twofold excess in lung cancer in the lower exposure categories, including those who worked with arsenic for less than a year, would not be ascribable to arsenic, because there was no change in cancer risk over a very wide range of total doses (0.04-1.36 g). Furthermore, these low dose categories consisted predominantly of short-term unskilled workers who as a group might have had higher exposures to other hazardous chemicals than the controls (The National Research Council, 1977a).

The Allied Chemical Company pesticide manufacturing operations produced a range of products, including some arsenical compounds. A preliminary study of the proportional mortality among retired employees showed a sevenfold excess of lung cancer that accounted for about 40% of all deaths. Both the Dow and Allied studies also showed a few excess deaths from lymphoma and Hodgkin's disease. The results of a more detailed study of the Allied Chemical Company that is now in progress will be very useful (The National Research Council, 1977a).

Arsenic sprays and dusts were widely used in Germany between 1925 and 1942, at which time they were banned (Braun, 1958; Roth, 1957b). Vineyard workers also drank wine containing arsenic. Hundreds of workers developed acute and chronic arsenic poisoning. In the 1950's, vineyard workers with lung cancer began to appear in hospitals serving the vineyard regions. An association between arsenic and lung cancer is further suggested by the high proportion of vineyard workers with lung cancer who had the characteristic hyperpigmentation and keratoses associated with chronic arsenic exposure (The National Research Council, 1977a).

The same high degree of association of skin arsenism and lung cancer occurred in Rhodesian gold miners who were heavily exposed to arsenopyrite dust (Osburn, 1969). In the period 1957-1963, the occurrence of 37 cases of lung cancer in gold miners represented an incidence of 206/100,000 compared with 34/100,000 for adult males in the Gwanda region of Rhodesia. This represents a sixfold difference in lung cancer in miners (The National Research Council, 1977).

The probability of death from lung cancer in persons with keratosis shown in Table 7, ranges from 32 to 56%, which is roughly 5-10 times higher than might be expected (The National Research Council, 1977a).

The data suggest that there is a very high risk of lung cancer when the exposure to inorganic arsenic dust is high enough to cause keratoses (The National Research Council, 1977a).

The only evidence that arsenic is a liver carcinogen comes from German vintners. Thirteen of the 27 persons whose autopsies were reported by Roth (1957) had cirrhosis, and three had angiosarcoma, a rare form of liver cancer associated with exposure to a vinyl chemical and Thorotrast. Only two cases of angiosarcoma have been reported in people treated with Fowler's solution (Regelson,et al. 1968). There is no evidence of either cirrhosis of liver damage in any of the other studies on arsenic. It is possible that the combined effect of a high alcohol intake and arsenic is responsible for the unusual forms of cirrhosis and liver cancer observed in vintners. It should also be pointed out that the chemical form of arsenic in wine is unknown (The National Research Council, 1977).

CRITERION FORMULATION

Existing Guidelines and Standards

In 1942, the U.S. Public Health Service set a maximum allowable level of 50 μg/liter for arsenic in drinking water supplied by interstate Carrier Water Supplies. The arsenic standard remained at that level in the 1962 revision of the Drinking Water Standards and has been continued in the U.S. Environmental Protection Agency Drinking Water Standards which became effective in June of 1977.

The American Conference of Governmental and Industrial Hygienists (1977) has set 0.5 mg/m^3 as the Threshold Limit Value-Time Weighted Average (TLV-TWA) for airborne arsenic. This means that the time weighted average concentration of airborne arsenic for a normal 8-hour workday or 40-hour workweek should not exceed 0.5 mg/m^3. The Conference has issued a Notice of Intended Change (for 1977) which will reduce the TLV-TWA from 0.5 mg/m^3 to 0.05 mg/m^3 (American Conference of Governmental and Industrial Hygienists, 1977).

The National Institute of Occupational Safety and Health has recommended a ceiling level of 2 μg/m^3 for airborne inorganic arsenic for any 15 minute period of the workday.

The new (August, 1978) Occupational Safety and Health Administration (OSHA) standard for airborne inorganic arsenic is 10 μg/m^3 TWA (Time Weighted Average).

Current Levels of Exposure

A broad range of arsenic levels have been found in drinking water samples. In a U.S. Environmental Protection Agency national study of residential tap water, 66.8 percent of the one time grab samples collected from 3834 residences had arsenic levels greater than 0.1 µg/liter. The average, minimum, and maximum levels of the samples with detectable arsenic were 2.37, 0.50, and 213.6 µg/liter, respectively (Greathouse and Craun, 1978; Greathouse, statistician -EPA, unpub.). In 1975 it was reported that 5 out of 566 samples collected from Interstate Carrier Water Supplies exceeded 10 µg/liter and that the maximum level was 60 µg/liter (U.S. Environmental Protection Agency, 1975). Well water samples collected during 1976 at 59 residences in a Fairbanks, Alaska suburban community had a mean arsenic content of 224 µg/liter with a range from 1.0 to 2,450 µg/liter (Public Health Service, 1977). Moderately elevated levels of arsenic, 10 to 330 µg/liter, are present in potable waters of some smaller communities in Utah, Nevada, and California (Valentine, project director-UCLA, personal communication). There have been a number of other reports of isolated instances of higher than usual concentration of arsenic in well waters (Goldsmith, et al. 1972; Feinglass, 1973; Morton, et al. 1976). The highest value reported in these studies was 21,000 µg/l in well water contaminated by arsenical grasshopper bait.

There is a wide diversity in the estimates of daily intake of arsenic in foods. Schroeder (1970) has estimated that the average diet provides an arsenic intake of about 1000 μg/day. Arsenic in a sample institutional diet amounted to about 400 ug/day (Schroeder and Balassa, 1966). This lower level is attributed, at least partially, to the absence of seafood, a primary source of arsenic, in the institutional diet. In contrast to these levels, the World Health Organization reported that average arsenic intakes for Canada, the United Kingdom, the United States, and France varied from 25 to 33 μg/day; specific values ranged from 7 to 60 μg/day (World Health Organization, 1973). A survey of food made in Great Britain indicated that 100 ug of arsenic would be consumed daily from all sources (Hamilton, 1972/1973).

According to Suta (1978), the levels of atmospheric arsenic in locations where major arsenic emitting sources are absent range from below the detection limit of 1 ng/m^3 to 83 ng/m^3 with an average of 3 ng/m^3. The annual average near major emission sources (copper, lead, and zinc smelters, cotton gins, pesticide manufacturers, and glass manufacturers) ranged from 3 ng/m^3 to 5,900 ng/m^3 with most below 290 ng/m^3. Assuming normal daily inhaled volumes of 21.2 and 11.1 cubic meters for men and women respectively, the ranges of daily airborne arsenic exposures in uncontaminated areas are 21-1, 760 ng and 11-921 ng for men and women respectively. In areas where arsenic emitting sources are located daily inhaled exposure levels may be as high as 6,148-125,080 ng and 3,219-65,490 ng for men and women, respectively.

No quantifiable information was found concerning present levels of exposure from drugs or dermal contact.

Special Groups at Risk

Adverse effects have been demonstrated in all age groups of both sexes.

Basis and Derivation of Criterion

As described in the Carcinogenesis Section, a number of studies have been shown that arsenic is important in the etiology of human cancers. Clinical, occupational, and population studies have demonstrated that both ingestion and inhalation exposures to arsenic compounds increase the risk of cancer induction in the tissues of the lung and skin and possibly other sites. There appears to be little question that arsenic is a human carcinogen, but there has been general failure to demonstrate this effect in any animal model. Hence, it is necessary to rely totally on human data rather than supplement it with appropriate animal toxicity and carcinogenic data. This limitation causes serious problems since animal studies are the only practical means to effectively evaluate relative toxicities, absorption rates, etc. for different compounds and routes of administration. Instead, these types of questions must be answered based on effects and observation of exposed populations recognizing the numerous unknowns (levels or arsenic and other environmental exposures, dietary patterns, genetic differences, etc.) and different routes of exposure.

The only study that relates levels of arsenic ingestion to skin cancer is the one conducted by Tseng (1968) in southwest Taiwan. He found a consistent dose response relationship between the exposure variable levels of arsenic in drinking water and age and skin cancer prevalence (Table 9). Questions concerning comparability between the U.S. and Chinese populations must be raised since some areas in the U.S. have similar arsenic levels without the reported dermatological manifestations. It is very possible that major differences in dietary patterns (the Chinese diet is low in protein and fat (Yeh, 1973), other environmental and/or occupational co-exposures, socio-economic status, etc. may account for the differences. However, since similar health responses have been observed in Antofagasta, Chile (Borgono and Greiber, 1972), Cordoba, Argentina (Bergoglio, 1964), German vineyard workers (Denk, et al. 1969), and those who ingest Fowler's Solution (Neubauer, 1947), it must be assumed that arsenic is at least one of the environmental exposures responsible for the observed effects. Secondly, the clear dose response relationships both by length of exposure, as indicated by age, and by level of waterborne arsenic provide additional evidence that arsenic is at least one of the agents responsible for the observed effects; it seems quite unlikely that other environmental, occupational, or socio-economic factors which might be responsible for variations in skin tumor incidence would have a similar gradient to the waterborne arsenic gradient. Hence, it appears reasonable to use the Taiwan data as a basis for estimating a level which will not increase the lifetime risk of cancer by more than 1/100,000; it is recognized the calculated level may be quite conservative since the Taiwan experience may represent a worst case situation due to other co-exposures and dietary deficiencies.

The EPA Cancer Assessment Group has developed a mathematical prediction model (Appendix I) for estimating an acceptable level based on the published Tawain data (Tseng, 1977). Their material is included in Appendix II to explain the model and the calculated estimates.

Under the Consent Decree in NRDC v. Train, criteria are to state "recommended maximum permissible concentrations (including where appropriate, zero) consistent with the protection of aquatic organisms, human health, and recreational activities." Arsenic is suspected of being a human carcinogen. Because there is no recognized safe concentration for a human carcinogen, the recommended concentration of arsenic in water for maximum protection of human health is zero.

Because attaining a zero concentration level may be infeasible in some cases and in order to assist the Agency and States in the possible future development of water quality regulations, the concentrations of arsenic corresponding to several incremental lifetime cancer risk levels have been estimated. A cancer risk level provides an estimate of the additional incidence of cancer that may be expected in an exposed population. A risk of 10^{-5} for example, indicates a probability of one additional case of cancer for every 100,000 people exposed, a risk of 10^{-6} indicates one additional case for every million people exposed, and so forth.

In the Federal Register notice of availability of draft ambient water quality criteria, EPA stated that it is considering setting criteria at an interim target risk level of 10^{-5}, 10^{-6}, or 10^{-7} as shown in the table below.

Exposure Assumptions (per day)	Risk Levels and Corresponding Criteria (1)			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 18.7 grams fish and shellfish. (2)	0	0.0002 μg/l	0.002 μg/l	0.02 μg/l
Consumption of fish and shellfish only.	0	0.01 μg/l	0.10 μg/l	1.0 μg/l

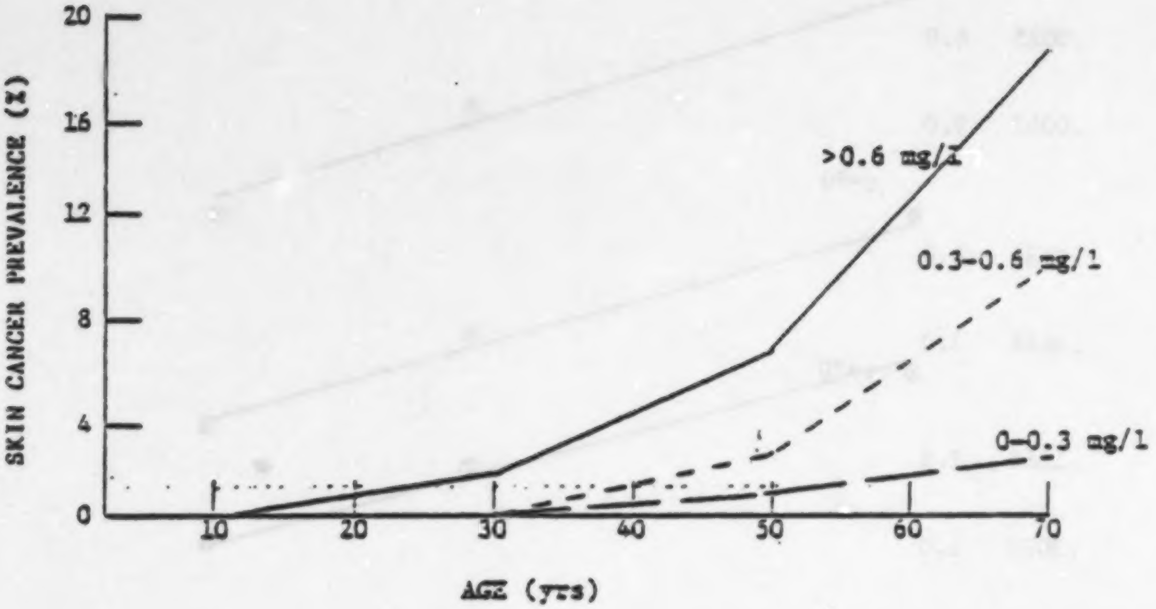
(1) Calculated by applying a modified "one-hit" extrapolation model described in the Methodology Document to the human epidemiological data presented in Appendix I. Since the extrapolation model is linear at low doses, the additional lifetime risk is directly proportional to the water concentration. Therefore, water concentrations corresponding to other risk levels can be derived by multiplying or dividing one of the risk levels and corresponding water concentrations shown in the table by factors such as 10, 100, 1,000, and so forth.

(2) 2 percent of the arsenic exposure results from the consumption of aquatic organisms which exhibit an average bioconcentration potential of 2.3-fold. The remaining 98 percent of arsenic exposure results from drinking water.

Concentration levels were derived assuming a lifetime exposure to various amounts of arsenic, (1) occurring from the consumption of both drinking water and aquatic life grown in waters containing the corresponding arsenic concentrations and, (2) occurring solely from consumption of aquatic life grown in the waters containing the corresponding arsenic concentrations.

Although total exposure information for arsenic is discussed and an estimate of the contributions from other sources of exposure can be made, this data will not be factored into ambient water quality criteria formulation until additional analysis can be made. The criteria presented, therefore, assumed an incremental risk from ambient water exposure only.

Figure 1



Prevalence of skin cancer with respect to age and arsenic concentration in well water for both sexes. (Tseng, et al. 1968)

Figure 2. Relationship Between Transformed Prevalence and log mg/l Arsenic in Water, log age

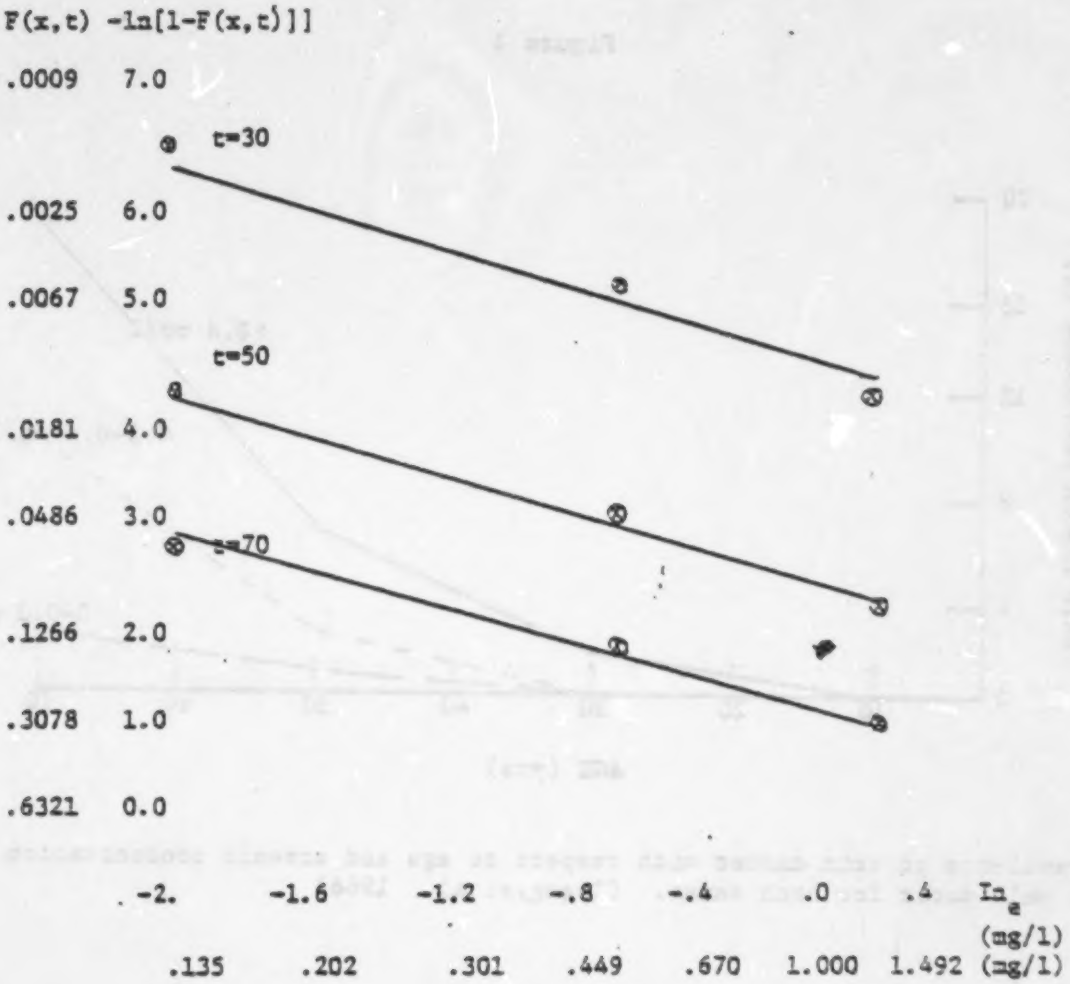


Table 1. Arsenic in Fresh Surface Waters

Water	Arsenic Concentration ug/liter (mg/l)	Reference
United States		
Lakes:		
New York, Chautauqua	3.5-35.6	Lis and Hopke, 1973
Michigan	0.5-2.4	Seydel, 1972
Superior	0.1-1.6	Seydel, 1972
Wisconsin	4.0-117	Chamberlain and Shapiro, 1969
California, Searles	198,000-243,000	White, et al. 1963
	0.0-100[a]	Livingston, 1963
	0.0-2,000[b]	Livingston, 1963
Florida, Echols	3.58	Braman and Foreback, 1973
Florida, Magdelene	1.75	Braman and Foreback, 1973
Rivers:		
Hillsborough	0.25	Braman and Foreback, 1973
Withlacoochee	0.42	Braman and Foreback, 1973
Fox (polluted watershed)	100-6,000	Brown, et al. 1973
Yellowstone	4.5	Ellis, 1934
Narrow	0.90	Ray and Johnson, 1972
Providence	0.75-0.90	Ray and Johnson, 1972
Seekonk	2.48-3.45	Ray and Johnson, 1972
Sugar Creek (contaminated)	<10-1,100	Durum et al. 1971: Wilder, 1972
Columbia	1.6	Onishi, 1969
Schuylkill	30-180	Kopp, 1967
Canals:		
Florida	<10-20	Grantham and Sherwood, 1968
Puget Sound	1.5-1,200	Crecelius, et al. 1975; Crecelius and Carpenter, 1974
Rainwater:		
Rhode Island	0.82	Ray and Johnson 1972
Washington, Seattle	17	Crecelius, et al. 1975
Chile	800	Borgono and Greiber, 1972
Formosa, well water	800	Fan and Yang, 1969

[a] Dissolved solids, <2,000 mg/l

[b] Dissolved solids, >2,000 mg/l

Table 2. Arsenic in Foods
(wet weight)

Food Sample	Arsenic Concentration (µg/1)	Micrograms of Arsenic per 100 cal[a]
Fish and sea food		
Haddock	2.17	305
Kingfish	8.86	886
Oysters, fresh	2.9	580
Oysters, frozen	2.7	540
Scallops, fresh	1.67	160
Shrimp, fresh frozen	1.50	132
Shrimp shells	15.3	
Clams, fresh frozen	2.52	525
Conch, fresh	3.1	311
Conch, dried, whole	5.63	311
Mean	4.64	417
Meats		
Beef, stewing	1.3	58
Pork loin	0.06	21
Pork liver, No. 1	1.07	75
Pork liver, No. 2	1.4	98
Pork kidney	0.0	0
Lamb chop	0.35	19
Chicken breast	0.0	0
Gelatin	0.19	6
Egg lecithin	0.0	0
Mean	0.49	36
Vegetables and grains		
Wheat, whole	0.17	5
Rye, seed	0.16	5
Corn	0.11	3
Corn meal	0.78	22
Corn oil	0.0	
Corn oil lecithin	0.0	
Rice, Madagascar	0.48	13
Rice, U.S.	0.13	3
Puffed rice	1.6	46
Kellogg's Special K	0.66	19
Cottonseed oil	0.0	
Beets	0.0	0

Table 2. Arsenic in Foods (Continued)
(wet weight)

Food Sample	Arsenic Concentration (µg/1)	Micrograms of Arsenic per 100 cal[a]
Vegetables and grains (cont'd)		
Beet greens	0.24	240
Swiss chard	0.56	215
Rhubarb	0.48	800
Red pepper	0.06	
Garlic, fresh	0.24	
Cherry tomatoes	0.37	264
Yellowpear tomatoes	0.10	70
Turnip	0.0	0
Mushrooms	2.9	414
Soy lecithin	0.0	0
Mean	0.41	125
Vegetables, St. Thomas, V.I.		
Carrots	0.0	0
Peas, dried	0.09	3
Peas, fresh	0.0	0
Tomatoes, fresh	0.0	0
Egg plant	0.82	546
Ginger	0.0	
Fruits		
Apple	0.0	0
Orange	0.0	0
Pear	0.0	0
Grapes, wild	0.17	34
Miscellaneous		
Cocoa, Hershey's	0.59	13
Coffee	0.0	
Tea	0.89	
Salt, table	2.71	
Salt, sea	2.83	
Sugar, lump	0.10	3
Sugar, granulated	0.0	0
Milk, evaporated	0.17	11
Milk, dry skimmed	0.0	0
Butter, unsalted	0.23	3

NOTE :

[a] Calorie values from McCance and Widdowson, 1947.

Source :

Modified from Schroeder and Balassa (1966).

Table 3. Bioaccumulation Ratio Values for Arsenic in Aquatic Organisms[a]

Species	Arsenic in tissue (μg/l)	Bioaccumulation ratio values[b]
Haddock	2-10.8	1,000-5,4000[c]
Kingfish	8.86	4,430
Crustacea and shellfish	1.5-3.1	750-1,550
	0.018-1.06	9-530
Assorted fish	0.076-2.27	38-1,135
Assorted fish	<1-6.4	<500-3,200[c]
Shrimp	3.6-48	1,836-64,100[c]
Mackerel	4.7-9.2	2,350-4,600[c]
Cod	24.3	12,150[c]
Assorted freshwater fish	0.1-0.2	10-20
	0.035-0.298	3-30[d]

Notes:

[a] Concentration in tissue/concentration in water.

[b] A marine concentration of 2 μg arsenic per liter is used in all calculations

[c] Dry weight basis.

[d] Water concentration assumed to be 10 μg arsenic per liter.

Source:

Modified from Woolson (1975). Data collected from several sources.

Table 4. Estimates of Population Exposures to Arsenic for Selected Emission Sources

Average Annual Concentration[a] (ug/m^3)	Emission Source Copper Smelters[b]	Lead Smelters[c]	Zinc Smelters[d]	Cotton Ginn[e]	Pesticide Manufacturer[f]	Glass Manufacturing[g]
3.0-5.9				5		
1.0-2.9	2,200			100		
0.60-0.99	--			200		
0.30-0.59	17,500			700		150
0.10-0.29	28,000	800	22,000	2,000		24,000
0.060-0.099	92,000	2,600	48,000	3,000		169,000
0.030-0.059	288,000	5,100	134,000	5,900		1,253,000
0.010-0.029	20,000	38,000	630,000	20,000	60	3,534,000
0.005-0.009	146,000	46,000	1,202,000	56,000	800	6,059,000
0.003-0.004	237,000	67,000	1,642,000	135,000	11,900	9,490,000

[a] Average omnidirectional concentrations. With the exception of cotton gin exposures, 24-hr worst-case exposures can be estimated by multiplying the annual averages of 12.5. The 24-hr worst-case exposures for cotton gins may be obtained by multiplying the concentrations by 81.

[b] Based on EPA's estimate of stack emissions. Assumes 10% fugitive emissions.

[c] Based on an emission of 0.5 lb of arsenic per each ton of lead produced. Fugitive emissions are estimated to be 10% of stack emissions.

[d] Based on an emission of 1.3 lb of arsenic per ton of zinc produced by pyrometallurgical smelters and no stack emissions at electrolytic smelters. Fugitive emissions assumed to be 10% of the 1.3 lb/ton stack emissions for all smelters.

[e] Annual average exposure, assuming that ginning exposures occur during 15% of the year and that there are no exposures during the remainder of the year.

[f] Assumes that all large plant pesticide emissions are well controlled.

[g] Assumes that 25% of pressed and blown glass is manufactured with arsenic and that only certain manufacturers use arsenic in all of their pressed and blown glass production.

Table 5. Arsenic Concentration and Prevalence of Pigmentation and Warts[a]

Workers	No. Persons	Arsenic Concentration (µg/l) Urine (µg/l)	Arsenic Concentration (µg/l) Hair (µg/l)	Prevalence, % Pigmentation	Prevalence, % Warts
Chemical workers	33	0.24	108	90	29
Maintenance workers and packers	32	0.10	78	38	3
Control[b]	56	0.09	13	18	4

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[a] Derived from Perry, et al.

[b] Including two former chemical workers.

Table 6. Death Due to Cancer, by Site[a]

Site	No. Cancer Deaths		Fraction of Cancer deaths, %[b]		Fraction of Total Deaths, %[b]	
	Factory Workers	Other 3 Occupational Groups	Factory Workers	Other 3 Occupational Groups	Factory Workers	Other 3 Occupational Groups
Buccal cavity and pharynx	2	10	9.1	6.4	2.7	0.8
Digestive organs and peritoneum	5	91	22.7	58.0	6.7	7.5
Respiratory organs	7	25	31.8	15.9	9.3	2.1
Genitourinary organs	2	13	9.1	8.3	2.7	1.1
Skin	3	2	13.6	1.3	4.0	0.2
Other or unspecified	3	16	13.6	10.2	4.0	1.3
Total	22	157	99.9	100.1	29.4	13.0

[a] Derived from Hill and Faning (1948).

[b] There were 75 deaths among the factory workers and 1,216 deaths in the other three occupational groups (see text).

Table 7.[a] Observed Deaths and Standardized Mortality Ratios (SMR) at Ages 65 and Over for the Period January 1, 1949, through December 31, 1973, among 530 Men Retiring from the Tacome Smelter by Cause of Death and Arsenic Exposure Index at Retirement[b]

Cause of Death	Arsenic Exposure Index[c] Total Obs	SMR	Under 3,000 Obs	OBS	3,000-5,999 Obs	SMR	6,000-8,999 Obs	SMR	9,000-11,999 Obs	SMR	12,000+ Obs	SMR
All causes	324	111.1[e]	87	98.1	124	110.3	70	129.2[e]	24	117.7	17	130.0
Cancer (140-205)	69	146.6[e]	15	107.9	28	156.0[e]	14	151.6	7	218.7	5	217.2
Digestive (150-159)	20	120.3	6	121.2	9	140.4	2	62.7	3	264.7	0	0.0
Respiratory (160-164)	32	300.3[e]	5	165.6	11	279.4[e]	7	306.9[e]	4	568.5[e]	5	810.5[e]
Lymphatic (200-203, 205)	2	94.9	1	166.1	1	126.1	0	0.0	0	0.0	0	0.0
Other cancer	15	84.8	3	56.3	7	102.8	5	150.4	0	0.0	0	0.0
Stroke (330-334)	44	114.7	18	150.3	12	80.0	7	104.5	6	218.4	1	64.7
Heart disease (400-443)	144	107.7	33	81.4	63	122.4	36	144.2[e]	5	53.6	5	83.2
Coronary (420)	118	105.9	25	74.9	52	122.2	31	145.1[e]	4	51.7	5	95.5
Other heart	26	116.6	8	111.5	11	123.2	5	138.4	1	62.9	0	0.0
Respiratory disease (480-493, 500-502)	10	91.6	4	116.8	3	70.9	1	52.4	2	250.8	0	0.0
All other causes.	57	91.2	17	89.2	18	74.8	12	104.1	4	91.3	6	212.4

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[a] Pinto, S.S., V. Henderson, and P. Enterline. "Mortality experience of arsenic exposed workers." Unpublished data.

[b] Expected deaths were estimated on the basis of Washington State experience, 1949-1970. Includes four men with unknown exposures.

[c] Arsenic exposure index derived from A. Baetjer, A.M. Levin, and A. Lilienfield, "Analysis of mortality experience of Allied Chemical plant," unpublished data.

[d] Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death (World Health Organization, 1957).

[e] Statistically significant ($p < 0.05$).

Table 8. Frequency of Lung Cancer in Persons with Keratoses Who Had Heavy Exposure to Arsenical Dusts

Subjects	(a) No. Cases of Keratosis	(b) No. Cases of Lung Cancer	b/a, %	Reference
Rhodesian gold miners	40	13	32	Osburn, 1969
Vintners (Braun)	16	9	56	Braun, 1958
Vintners (Roth)	30	10	33	Roth, 1957
Sheep-dip workers[a]	12	5	42	Perry, et al. 1948
Total	98	37	38	

[a] Assumes that 41 chemical workers who died in 1910-1943 had the same skin changes as chemical workers examined in 1946.

Table 9.

AGE - EXPOSURE - SPECIFIC Prevalence Rates

(mg/l)	20-39 (30)	40-59 (50)	>60 (70)
0 - .29 (0.15)	0.0013	0.0065	0.0481
0.30-0.59 (0.45)	0.0043	0.0477	0.1634
≥0.6 (1.2)	0.0224	0.0983	0.2553

Table 10. Data Utilized to Obtain Predictor Equation and Figure 2

mg/l Arsenic	Age at Medical Examination	Skin Cancer Prevalance Rate		Transformed Skin Cancer Prevalance Rate	
x	t	F(x,t)		$-\ln[-\ln[1-F(x,t)]] = -17.5393 + 3.8531\ln t+\ln x$	
		Observed Rate	Expected Rate	Observed	Expected
15	30	.0013	.0031	6.64474	6.33160
	50	.0065	.0127	5.03269	4.36341
	70	.0481	.0455	3.00993	3.06695
.45	30	.0043	.0053	5.44699	5.23299
	50	.0477	.0375	3.01849	3.26480
	70	.1634	.1304	1.72368	1.96834
1.20	30	.0224	.0141	3.78739	4.25216
	50	.0983	.0969	2.26844	2.28397
	70	.2553	.3110	1.22155	.98751

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APPENDIX I - MATHEMATICAL PREDICTION MODEL FOR ARSENIC

Due to the stable population in a rural area along the southwest coast of Taiwan, the data collected by Tseng et al. (1968) may be viewed as a lifetime feeding study where measured amounts of arsenic in well water are consumed by a study population of 40,421 individuals. Thus, this data may be used to predict the lifetime probability of skin cancer caused by the ingestion of arsenic.

A model estimating the cancer rate as a function of drinking water arsenic concentration was generated using the information in its published form, which is a summary of data collected by the investigators. If the original data had been available, a more exact mathematical analysis would have been possible.

Doll (1971) has suggested that the relationship between the incidence of some site specific cancers, age, and exposure level of a population may be expressed as

$$(1)\ I\ (x,t) = vBx^{m}t^{v-1}$$

where x is the exposure level of a carcinogen, t is the age of the population, and B, m, v are unknown parameters.

However, the data collected by Tseng et al. (1968) was obtained at one point in time, and since skin cancer has only a marginal effect on the death rate, the obtained rates may be viewed more accurately as the probability of having contracted skin cancer by time t. The relationship between this probability, often referred to as the cummulative probability density or prevalence, and the incidence or age specific or hazard rate may be expressed as

$$(2)\ F\ (x,t) = 1 - \exp\ [\int_{0}^{t} I(x,s)\ ds]$$

Utilizing the suggestion of Doll (1971) for the form of the incidence rate, the prevalence may be expressed as

$$(3)\ F\ (x,t) = 1 - \exp\ (-Bx^{m}t^{v})$$

which is a Weibull distribution.

Fixing m = 1 we have the relationship

$$(7)\ F(x,t) = 1 - \exp[g(t)x]$$

Transforming this equation to its linear form and obtaining the least square estimates of B and v, we find that

$$g\ (t)=\exp(-17.5393)\ t^{3.853},\ \text{where } B = 2.41423 \times 10^{-8},\ v=3.853$$

In this case, the fit is still quite good as represented by a correlation of 0.971. The data used to obtain the estimates is shown in Table 10 and the goodness of fit is illustrated in Figure 2.

The function $F(x,t) = 1-\exp[-2.41423\ 10^{-8} x\ t^{3.853}]$, is the probability of contracting skin cancer by age t given that an individual had a lifetime exposure to x mg/l in his drinking water (and lived until age t).

In Appendix I of the CAG (1978) coke oven document the lifetime probability of cancer in the presence of competing mortality was derived from the age-specific incidence rate. For the case where the cancer rate in the absence of exposure is near zero (as in this case where the skin cancer is of a rare form that was virtually unknown in other parts of Taiwan) the lifetime probability may be expressed as

$$Q_2(\ ) = Bx/(Bx+p^{v})$$

where $p^{v} = \ln 2\ t_m^{\ v}$, (where t_m is the median lifetime of the population). Assuming $t_m=68$ and $v=3.853$, is the same for total mortality as the appearance of skin cancer we have that

$$Q_2(\ ) = \frac{2.41423\ x}{2.41423\ x + 6.02793}$$

The level of x that results in a lifetime probability of skin cancer equal to 10^{-5} is found by solving $Q_2(\ ) = 10^{-5}$ for x giving $x=2.4969 \times 10^{-5}$ mg/liter or 0.025 μg/liter.

Under the assumption that the average consumption of water is two liters in both the U.S. and Taiwan we estimate a water criteria concentration of:

$$2(.025) = S(2 + .0187 \times 2.3) \text{ \underline{or}}$$

$$S = \frac{.05}{2.0430} = .02447$$

Where .0187 is the average fish consumption in kilograms and 2.3 is the bioaccummulation factor for fish (supplied by Don Mount of U.S. EPA).

A criterion for waterborne arsenic of .02 μg/l would thus insure a lifetime risk of cancer of less than 10^{-5}.

It is recognized that inorganic and organic compounds differ in terms of toxicity and likely in terms of carcinogenic potential. However, since the recommeded level is to be based on carcinogenic potential and no information is available concerning the relationship(s) of specific arsenic species and cancer a single all inclusive limit must be set. Even if the data were available to permit separate standards, the level of development of the required analytical methodology is not sufficient to permit reliable and repeatable speciation measurements, a necessity before setting a standard (personal communication with Dr. Irgolic at Texas A&M University).

For comparative purposes, the Stockinger and Woodward (1958) method was applied to the present and proposed airborne arsenic standards to compute comparable waterborne arsenic levels.

American Conference of Governmental Industrial Hygienists:

1. Existing Threshold Limit Value - Time Weighted Average -500 μg/m^3

$$\frac{500 \text{ ug}}{\text{m}^3} \times 10 \text{ m}^3 \times \frac{5 \text{ days}}{\text{week}} \times 20\% \text{ absorption} = 5{,}000 \text{ μg/liter}$$

$$\frac{5000 \text{ ug}}{\text{week}} \times \frac{1 \text{ week}}{7 \text{ days}} \times \frac{1}{2 \text{ Liters}} \times \frac{\text{Allowed}}{80\% \text{ absorption}} = 446 \text{ μg/liter}$$

Applying the recommended safety factor of 1/100 the comparable drinking water limit is 4.46 ug/liter.

2. Proposed Threshold Limit Value - Time Weighted Average -50 ug/m^3

$$\frac{50\ \mathrm{ug}}{\mathrm{m}^3} \times 10\ \mathrm{m}^3 \times \frac{5\ \mathrm{days}}{\mathrm{week}} \times 20\%\ \mathrm{absorption} = 500\ \mathrm{ug/wk}$$

$$\frac{500\ \mathrm{ug}}{\mathrm{week}} \times \frac{1\ \mathrm{week}}{7\ \mathrm{days}} \times \frac{1}{2\ \mathrm{liters}} \times \frac{\mathrm{Allowed}}{80\%\ \mathrm{absorption}} = 44.6\ \mathrm{ug/liter}$$

Applying the recommended safety factor of 1/100 the comparable drinking water limit is 0.45 µg/liter.

Occupational Safety and Health Administration

1. Eight-hour average - 10 µg/m^3

$$\frac{10\ \mathrm{ug}}{\mathrm{m}^3} \times 10\ \mathrm{m}^3 \times \frac{5\ \mathrm{days}}{\mathrm{week}} \times 20\%\ \mathrm{absorption} = 100\ \mathrm{ug/week}$$

$$\frac{100\ \mathrm{ug}}{\mathrm{week}} \times \frac{1\ \mathrm{week}}{7\ \mathrm{days}} \times \frac{1}{2\ \mathrm{liters}} \times \frac{\mathrm{Allowed}}{80\%\ \mathrm{absorption}} = 8.93\ \mathrm{\mu g/liter}$$

Applying the recommended safety factor of 1/100, the comparable drinking water limit is 0.08 µg/liter.

Assuming that the absorption factors (air-20%, water-80%) and methods recommended by Stockinger and Woodward (1958) are reasonable and that the safety of 1/100 is appropriate, it is clear that the recommended water standard is even more restrictive than the air standards. The differences are likely due at least partially to variations in extrapolation methods and levels of acceptable risk.

It is of interest to see what cancer risk would be associated with an air exposure equivalent to the recommended criterion of .02 ug/l. If we make the following assumptions:

(1) Total daily average absorbed arsenic from water is

$.8 \times .02\ (2 + .0267 \times 15) = .0384$ ug, where 80% is the absorption rate.

(2) The breathing rate is 1m^3/hr and 20% of the arsenic is absorbed.

Then, the air concentration, X, required to obtain the same absorbed amount of arsenic is

$$.2 \times 24 \times X = .0384 \text{ mg} \quad \underline{\text{or}}$$

$$X = .008 \text{ ug/m}^3$$

From the 1978 CAG report on the risk associated with airborne arsenic the lifetime cancer risk associated with X ug/M^3 of arsenic in the air is estimated to be

$$P = 3.418 \times 10^{-3} X$$

If instead of basing our risk on the most sensitive study we use the geometric mean of the three studies the lifetime cancer risk would be

$$P = 1.95 \times 10^{-3} X$$

The risks associated with $X = .008$ are thus 2.73×10^{-5} and 1.56×10^{-5}. Thus if our water criterion was based on the geometric mean of the human epidemiological air studies it would be .013 ug/l instead of .02 ug/l, which is a remarkably consistent result.